

Pleural Effusion - A Clinical and
Cytological Study

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By

Ronald Foote Robertson

M.B. (Hons.), F.R.C.P. Ed., M.R.C.P.

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SECTION I
INTRODUCTION

It is customary to introduce a thesis with an historical review of the subject under consideration. The history of pleural effusion, however, has already been set out in detail by Maclean (1948), to whose paper the reader is referred. When the subject of the thesis is one about which there is already extensive literature, it is next customary to give a reason for adding to this literature. With regard to pleural effusion, the author can put forward only the mundane reason of a long-continued interest in the subject along with the excuse that certain problems relating to it seemed in need of further investigation and, if possible, elucidation.

It is not proposed in the introduction to refer in detail to those problems, since each is elaborated in due course. It should be stated, however, that the author's studies have been conducted for the most part in medical units and ancillary departments of a general hospital, so that the problems are those encountered by a general physician in the course of his every-day work. There is thus, for example, no reference to pleural effusion complicating artificial pneumothorax therapy for pulmonary tuberculosis, and only indirect reference to special investigations

such as bronchoscopy and thoracoscopy which are normally performed at a thoracic surgical unit to which the patient is transferred.

The term "pleural effusion" can be, and often is, applied to any collection of fluid in the pleural cavity. In this thesis, however, the term is held to exclude empyema and, excepting some reference to difficulties in differential diagnosis, passive transudate (hydrothorax). Frequent reference is made to primary tuberculous pleural effusion. By this is meant tuberculous pleurisy with effusion occurring in the absence of the "adult" form of pulmonary tuberculosis, and commonly thought to be the result of a primary tuberculous infection in the lung and mediastinal glands occurring some months previously.

Comment is required on the arrangement of the thesis. A division into Sections has been made to facilitate cross-references. Each Section has been written so that, with respect to the problem discussed, it is more or less complete in itself; this has led to a certain, but, it is hoped, not undue amount of repetition among the Sections. The order of Sections has been determined with only one object in mind, namely that information derived from earlier Sections might be available for application to the problems discussed in later Sections. Since a large

part of the work has consisted of clinical observation of patients, many case reports are necessary; to save space and to avoid unnecessary tedium, such reports are in a form which gives only essential information. Tables are arranged as integral parts of the text. Figures are numbered, and, with the exception of those in the Section on Cytology, are inserted on un-numbered pages at convenient places in the text.

SECTION IICYTOLOGICAL INVESTIGATION OF PLEURAL FLUID

From the diagnostic point of view, the cytological investigation of pleural fluid falls into two compartments

(A) study of the distribution of polymorphs, lymphocytes and serosal cells

(B) search for malignant cells.

The former is technically easy and can be carried out by the physician or even by a trained laboratory technician. The latter is usually regarded as a formidable procedure requiring the services of a skilled pathologist or even of a specially trained cytologist. The work presented in this section was undertaken for the purpose of assessing the value of both (A) and (B) using relatively simple methods applicable to the routine investigation of cases of pleural effusion in a general hospital served by a Pathology department the staff of which does not include a special cytologist.

(A) Study of the Distribution of Polymorphs,
Lymphocytes and Serosal Cells.

Since the original work of Widal and Ravaut (1900), it has been accepted and taught that in pleural fluid predominant lymphocytes mean tuberculosis, predominant polymorphs mean simple inflammation and predominant serosal cells mean a mechanical cause such as malignancy, cardiac failure or

pulmonary infarction. In the course of the years, an occasional voice has been raised against this simple teaching; Miller (1904) found a study of the cells in 75 pleural (and ascitic) fluids of "little help"; Sahli (1911) advocated "a critical attitude, not a single cell picture being pathognomonic"; Feldman and Lewis (1946) stated more specifically that 6 of 57 tuberculous fluids contained polymorphs in excess; Phillips and McDonald (1948) found that lymphocytes predominated in all serous fluids irrespective of aetiology; Nairn (1949) referred to 3 simple inflammatory fluids with lymphocytes predominating, although eventually each fluid became an empyema.

The doubts so expressed can readily be confirmed by cytological examination of a reasonable number of fluids, as will be shown. The problems are whether the exceptions to the teaching of Widal and Ravaut are sufficiently numerous to be significant and whether a more careful study can find a way round the difficulties which occur. With those problems in mind, the author examined by a uniform technique 146 serous pleural fluids from 146 patients under personal observation in the Royal Infirmary of Edinburgh. The diagnosis of the cause of the fluid was in each patient established with certainty or beyond reasonable doubt by methods other than cytological examination of the fluid. Patients in

whom the diagnosis remained in doubt were excluded in the final analysis. Table 1 shows the distribution according to diagnosis.

TABLE 1

Diagnosis in 146 Cases of Serous Pleural Effusion

Diagnosis		No. of Cases	
Tuberculosis	: Post-Primary	92)	96
"	: Adult Type	4)	
Neoplasm	: Primary Bronchial	14)	29
"	: Primary Elsewhere	11)	
"	: Reticulosis	4)	
Simple Inflammation			12
Cardiac Transudate			7
Pulmonary Infarction			2
Total			146

Description of Technique of Cytological Examination.

1. Fluid was aspirated as soon as possible after the admission of the patient to hospital, or, in a few cases, as an out-patient.
2. 10 c.c. of fluid in a specimen tube was prevented from clotting by the addition of 0.5 c.c. 3.8% sodium citrate.

A total cell count can be done on this specimen by the same technique as for a white blood cell count; the total count, however, varies so widely (100 - 5000 per cu.mm.) in all types of fluid that it is probably of no value diagnostically and can therefore be omitted.

3. The specimen was centrifuged at moderate speed for 5 minutes, so producing a deposit of cells at the bottom of the centrifuge tube. An obvious deposit was obtained in all cases except a few of the transudates in which the number of cells was small. The deposit was invariably red in colour due to red blood cells even when the fluid on aspiration showed no trace of blood-staining.

4. The supernatant fluid was simply removed by inverting the centrifuge tube, the deposit of cells remaining stuck to the tube.

5. The deposit was caught up on a wire loop and spread on each of three clean glass slides, films of varying thickness being made.

6. Each film was fixed by heating the slide in a Bunsen flame.

7. For staining, after preliminary trials with various stains, Leishman's stain was found most satisfactory. The method used was the same as for a blood film, but with doubled times - i.e. 2 minutes undiluted and 10 minutes diluted.

8. The films were examined mainly with an oil-immersion lens. The thinnest film was used for an accurate differential count, 200 cells being counted. Numerous red blood cells were present in all the films examined.

9. Lymphocytes and polymorphs were easily identified. It was originally hoped that malignant cells might

also be recognised, but experience proved conclusively that the Leishman film was useless for this purpose. Malignant cells did not stain with sufficient detail to enable differentiation to be made from innocent serosal cells. Hence it was decided, in the differential counts, to include under the term "serosal cells" all cells which were not lymphocytes or polymorphs, and which might be either true serosal cells or malignant cells.

10. In some cases, extra tubes of fluid were withdrawn and deliberately left unexamined for varying intervals of time to determine whether disintegration of cells occurred sufficiently to render examination difficult or impossible. It was found that delay up to 24 hours had no appreciable effect in this respect.

Analysis of the Tuberculous Fluids:

Total 96. 9 were lightly blood-stained and 1 heavily blood-stained on initial aspiration. 6 were slightly more hazy than the usual clear serous effusion.

TABLE 2 /

TABLE 2Distribution of Lymphocytes, Polymorphs and Serosal Cells in 96 Tuberculous Pleural Fluids

Cells Per Cent	No. of Fluids		
	Lymph.	Polym. (1)	Serosal
90 - 100	64	2	0
80 - 89	10	1	0
70 - 79	7	0	0
60 - 69	6	0	0
50 - 59	3	2	1
40 - 49	2	0	1
30 - 39	1	3	2
20 - 29	0	5	4
10 - 19	1	7	14
0 - 9	2	76	74
	96	96	96

Note (1). The term includes neutrophils, eosinophils and basophils. In 6 fluids eosinophils were observed, varying in number from less than 1% (2), to 1% (2), 3% (1) and 6% (1). In 3 fluids basophils were observed, all less than 1%.

It is evident from the table that not all tuberculous fluids show a predominance of lymphocytes; at the same time, the exceptions are not numerous. In the 74 fluids with lymphocytes more than 80%, most of the remaining cells were serosal cells except in one fluid which had 14% polymorphs.

In the 22 fluids with lymphocytes less than 80%, the cells replacing the lymphocytes were mainly polymorphs in 12 fluids, mainly serosal cells in 6 fluids and an equal number of polymorphs and serosal cells in 4 fluids.

Of more interest and importance is a brief review of the fluids showing more than 20% polymorphs since it is in them that diagnostic difficulties tend to arise. There were 13 such fluids, all post-primary in type, which are now listed with the actual percentage of polymorphs and brief notes regarding the clinical type of case.

<u>Case</u>	<u>Polymorphs Per Cent</u>	<u>Clinical Notes</u>
1	20	very acute; died later pulm. T.B.
2	21	very acute; died later pulm. T.B.
3	25	mild; rapid recovery.
4	26	very acute; died later pulm. T.B.
5	28	very acute; progressive primary in lung.
6	30	very acute; slow recovery.
7	35	very acute; eventual bilat. effusion.
8	36	very acute; died later miliary T.B.
9	52	relatively mild; rapid recovery.
10	58	very acute; slow recovery.
11	85	very acute; eventual miliary and spinal T.B.
12	94	very acute; eventual T.B. empyema and pulm. T.B.
13	98	very acute; eventual pulm. T.B.

None of the 13 fluids was blood-stained. No. 12, which eventually became a tuberculous empyema, was slightly more hazy than the usual serous effusion, but could not be called turbid.

It may be significant that of the 13, 11 were due to a very acute illness with marked toxæmia and rapid formation of fluid. The subsequent fate of the 13 patients is also of interest: 8 developed serious tuberculosis and 3 more had a prolonged illness which gave rise to anxiety. Those facts are merely recorded: no statistical deductions can be made.

Only 8 of the 96 fluids had more than 20% serosal cells, reaching a maximum of 50% in one fluid. The 8 fluids were unexceptional in their naked-eye appearance; the 8 patients had mainly subacute illnesses clinically.

Analysis of the Neoplastic Fluids:

Total 29. 9 were heavily blood-stained on initial aspiration.

TABLE 3Distribution of Lymphocytes, Polymorphs and Serosal Cells in 29 Neoplastic Pleural Fluids

Cells Per Cent	No. of Fluids		
	Lymph.	Polym. (1)	Serosal (2)
90 - 100	2	0	4
80 - 89	3	0	3
70 - 79	5	0	3
60 - 69	3	0	0
50 - 59	4	0	4
40 - 49	1	1	1
30 - 39	3	2	4
20 - 29	3	2	3
10 - 19	1	3	3
0 - 9	4	21	4
	29	29	29

Note (1). 2 fluids had an occasional eosinophil.

(2). As previously explained, this term includes malignant cells if present.

Compared with Table 2 - tuberculous fluids - important features are:-

i. The much greater "scatter" of lymphocytes through the whole range 0 - 100%.

ii. The number of fluids (10 of 29) with serosal cells more than 60% - no tuberculous fluid showed such a high figure.

iii. The absence of a very high percentage of

polymorphs.

iv. As might be expected, a lymphocyte count falling below 80% was associated in nearly all instances with an increase of serosal cells rather than polymorphs.

Analysis of Simple Inflammatory Fluids:

Total 12. 2 were slightly blood-stained on initial aspiration. 3 were slightly hazy, but not turbid. All were sterile on culture.

TABLE 4

Distribution of Lymphocytes, Polymorphs and Serosal Cells in 12 Simple Inflammatory Pleural Fluids

Cells Per Cent	No. of Fluids		
	Lymph.	Polym. (1)	Serosal
90 - 100	1	2	0
80 - 89	0	2	0
70 - 79	0	0	0
60 - 69	0	1	0
50 - 59	2	2	0
40 - 49	2	2	2
30 - 39	1	0	0
20 - 29	1	2	3
10 - 19	3	0	1
0 - 9	2	1	6
	12	12	12

Note (1). 1 fluid had 58% eosinophils and 1% basophils. 1 fluid had 82% eosinophils.

(See discussion later on pleural eosinophilia)

It is observed that only 1 fluid had a very high lymphocyte count, but it proved a most important exception; later the lymphocytic exudate changed to a polymorphous exudate, and the originally serous fluid became an empyema; at subsequent operation with pleural biopsy, no evidence of tuberculosis was found.

Of the 12 fluids, 5 had polymorphs less than 50%, the remaining cells being mainly lymphocytes.

Of the 2 fluids with 40% serosal cells, one was of exceptional interest, the actual differential count being lympho. 2%, polym. 58%, serosal 40%. This was the only fluid in the whole series of 146 showing a high percentage of both polymorphs and serosal cells; the fluid was a clear sterile collection secondary to a subphrenic abscess; one is tempted to postulate a combination of infection and mechanical irritation, such as might occur with subphrenic abscess, to explain this obviously uncommon cytological picture.

Analysis of Cardiac Transudates:

Total 7. 1 was slightly blood-stained on initial aspiration.

TABLE 5Distribution of Lymphocytes, Polymorphs and Serosal Cells in 7 Cardiac Transudates

Cells Per Cent	No. of Fluids		
	Lymph.	Polym.	Serosal
90 - 100	1	0	0
80 - 89	1	0	0
70 - 79	1	0	1
60 - 69	0	0	1
50 - 59	0	0	0
40 - 49	0	0	1
30 - 39	1	1	1
20 - 29	2	1	1
10 - 19	1	1	2
0 - 9	0	4	0
	7	7	7

The features of this table are precisely the same as those of Table 3 - neoplastic fluids - namely the "scatter" of lymphocytes through the whole range 10 - 100%, the absence of a very high percentage of polymorphs, and the occurrence of fluids containing over 60% of serosal cells.

Analysis of Pulmonary Infarction Fluids:

Total 2. None blood-stained.

	<u>Lymph. %.</u>	<u>Polym. %.</u>	<u>Serosal %.</u>
(1)	64	4	32
(2)	70	0	30

The moderate number of serosal cells is noted.

Combined Analysis of 146 Fluids:

The following table, although superficially somewhat complicated, is perhaps the best way of presenting the results from the practical diagnostic point of view. Each type of cell is considered as a progressively falling percentage and opposite the percentage is the number of fluids in each group accumulating with each fall.

TABLE 6Combined Analysis of 146 Fluids

Cell and Progressive Percentage Fall	Fluid Group (No. of Cases)				
	T.B. (96)	Malig. (29)	Inflam. (12)	Trans. (7)	Infarct. (2)
<u>Lymphocytes</u>					
90 - 100	64	2	1	1	0
80 - 100	74	5	1	2	0
70 - 100	81	10	1	3	1
60 - 100	87	13	1	3	2
50 - 100	90	17	3	3	2
<u>Polymorphs</u>					
90 - 100	2	0	2	0	0
80 - 100	3	0	4	0	0
70 - 100	3	0	4	0	0
60 - 100	3	0	5	0	0
50 - 100	5	0	7	0	0
40 - 100	5	1	9	0	0
30 - 100	8	3	9	1	0
<u>Serosal Cells</u>					
90 - 100	0	4	0	0	0
80 - 100	0	7	0	0	0
70 - 100	0	10	0	1	0
60 - 100	0	10	0	2	0
50 - 100	1	14	0	2	0
40 - 100	2	15	2	3	0
30 - 100	4	19	2	4	2

From this table, the following comments and conclusions can be stated:-

1. Serosal cells, including, as previously defined, cells which may be malignant cells, provide, albeit in a limited number of cases, the most certain help in diagnosis -

(a) a count of over 80% occurred only in neoplastic fluids, of which a reasonably high proportion (7 out of 29) showed this finding.

(b) a count of over 60% occurred only in neoplastic fluids and transudates.

(c) a count of over 50% still occurred mainly in neoplastic fluids and transudates, but at this level the presence of a single tuberculous fluid indicated that the critical point had been passed.

2. Lymphocytes are of little diagnostic value in the individual case. Although a count of over 90% is strongly in favour of tuberculosis, the occasional case of neoplasm, transudate and even simple inflammation may fall within this percentage. Lowering the figure in a limited manner to 80% brings in an appreciable number of neoplastic fluids.

3. Polymorphs require careful interpretation. A count of over 90%, while favouring simple inflammation, can occasionally occur in tuberculosis. In this series, a count of over 50% indicated simple inflammation or tuberculosis, and did not occur in

neoplasm, transudate or infarct. It should be kept in mind, however, that a bronchial neoplasm may be complicated by simple inflammation of the lung and pleura; hence, if on other grounds tuberculosis is considered unlikely, a polymorph count of over 50% can be attributed to simple inflammation with the proviso that there may be a neoplastic background.

Cytological Examination Repeated after an Interval:

This was done on a limited number of fluids which required further aspiration(s) for diagnostic or therapeutic purposes. On the whole, the distribution of lymphocytes, polymorphs and serosal cells remained remarkably constant in each fluid over a period of weeks, but two notable exceptions, deserving further comment, occurred:

1. A clear, sterile simple inflammatory effusion initially had almost 100% lymphocytes; in the course of several weeks the clear effusion became an empyema with change of cells to almost 100% polymorphs.
2. A clear, sterile post-primary tuberculous effusion changed as follows:-

		<u>Lymph.</u>	<u>Polym.</u>	<u>Serosal</u>
8.10.51	(initial aspiration)	36	52	12
17.10.51	(second ")	66	26	8
9.11.51	(third ")	97	1	2

Several points for discussion arise. A lymphocytic exudate becoming polymorphous may indicate increasing infection in an originally

sterile simple inflammatory effusion, as in case 1., but it may also indicate the development of a tuberculous empyema from, or secondary infection of, an ordinary clear tuberculous effusion. Hence this change of cytology, while helpful in indicating the development of a serious clinical condition, would not seem particularly helpful in indicating the aetiology of the original effusion. On the other hand, secondary infection of a clear tuberculous effusion was not observed in the author's series and must be nowadays exceedingly rare; so too, the only tuberculous fluid to become a tuberculous empyema was polymorphous from the beginning.

A polymorphous exudate becoming lymphocytic may indicate an acute tuberculous infection becoming less acute, as in case 2. In theory it may also indicate a simple inflammatory effusion subsiding either spontaneously or under the influence of anti-biotic therapy; this theoretical possibility has not been observed in the author's series, mainly because the simple inflammatory fluids commonly absorbed so quickly that repeat cytological studies could not be done; in the few which were repeated, polymorphs either remained the same or increased. It is probably reasonable to state that a change from polymorphs to lymphocytes in an effusion which is increasing in quantity is a point strongly in favour of tuberculosis.

Change in Cytology following Intra-pleural Medication.

Intra-pleural medication was employed in only one case of the series. 2 Gms. of para-amino-salicylic acid (P.A.S.) in 10 c.c. saline was injected into a primary tuberculous effusion showing lymph. 96%, polym. 1%. and serosal 3%.; aspiration was repeated 48 hours later and the fluid now showed lymph. 51%, polym. 49%. and serosal 0%.; the fluid remained sterile on culture. There is little doubt that the increase in polymorphs was due to the action of P.A.S., and some anxiety was felt lest the increase heralded the development of a tuberculous empyema. The patient, however, made a normal recovery from her illness.

Fluids not included in the main series of 146.

Apart from the 146 fluids already analysed in detail, Leishman film studies were made on certain other fluids. In some of those the aetiology of the fluid was not satisfactorily established; in isolated cases, unsuitable in number for analysis, the fluid was due to trauma, collagen disease and Meig's syndrome. Such fluids commonly showed a non-specific lymphocytic exudate. Certain fluids, including two already referred to as "simple inflammatory" in origin, showed an extraordinarily high percentage of eosinophils; it was thought advisable, partly for convenience and partly because

of their unusual nature and possible doubt regarding diagnosis, to consider them as a group separate from the main analysis.

Fluids Containing a High Proportion of Eosinophils
(Pleural Eosinophilia)

Referring to the cytology of the pleural fluid in sero-fibrinous pleurisy, Price (1946) states that (a) "in rare cases large numbers of eosinophils have been found" and (b) "the origin of these cases is at present doubtful". The rarity of the condition is also emphasised by Kirk (1938) who did not find a single instance in 160 cases of pleural effusion examined cytologically, and by Bayne-Jones (1916) who states that from 1 - 5% of fluids may be eosinophilic, the exact figure depending upon the minuteness of staining and examining the sediment.

There is some uncertainty in the literature regarding the precise definition of eosinophilic pleural fluid. MacMurray, Katz and Zimmerman (1950) consider that a fluid can be termed eosinophilic if 5% or more of the cells (other than red blood cells) are eosinophils. Most of the reported cases, however, indicate that typical eosinophilic fluid has an eosinophil content of at least 50% and sometimes as high as 90%. In the present uncertain state of knowledge regarding the significance of eosinophilic fluid, it would seem wise to limit the term to undoubted and striking cases with a high percentage

of eosinophils, thus excluding the not uncommon cases in which a few eosinophils, possibly derived from extravasated blood and almost certainly of no special significance, are observed. It is also important, in suspected eosinophilic fluid, to avoid errors in identification of the cells present. This is emphasised, because with Leishman's stain, which is commonly employed for simple cytological investigations, the granules of neutrophil polymorphs may appear unduly pink, thus simulating, on superficial examination, the granules of eosinophils; confusion can be avoided by careful observation for the typical bilobed nuclei of eosinophils. Further it should be ascertained that the fluid is really pleural fluid - Trail (1943) has pointed out that eosinophilic fluid may be aspirated from a pulmonary hydatid cyst which has been diagnosed in error as a pleural effusion.

The study presented in this sub-section is based on 8 cases of pleural eosinophilia encountered during the Leishman film investigation of 163 pleural fluids, including the 146 already analysed, an incidence of 4.9 per cent. In all 8 cases, the proportion of eosinophils in the fluid was over 50%. It is of interest that of all the other fluids, only 8 contained any eosinophils, the proportions being less than 1% (5), 1% (2), 3% (1) and 6% (1). This indicates that when true pleural eosinophilia does

occur, it is likely to be a striking phenomenon.

Essential details of the cases are as follows.

Case 1. Mrs. E.H. aged 27 gave birth to a child on 16th July, 1947. On the 15th day of the puerperium she developed acute pleuritic pain in the left chest, followed 3 days later by haemoptysis. At this point she was admitted to a medical ward. Clinical and radiological examination of the chest showed a small left pleural effusion without evidence of parenchymatous lung disease. Diagnostic aspiration of the pleural fluid gave the following findings:- Clear serous fluid with thin clot; cell count 900/cu.mm.; differential count - eosinophils 52%, neutrophils 8%, lymphocytes 18%, serosal cells 22%; ordinary culture - sterile; Lowenstein-Jensen culture - sterile. Aspiration was repeated after three weeks with similar findings, although by now the eosinophils showed marked degenerative changes. Several blood counts showed no blood eosinophilia. X-ray of chest following absorption of the fluid showed no lung pathology. A Mantoux test (1:100) was negative, and has remained so during a five year follow-up. The final diagnosis was pulmonary embolism with associated pleural effusion following pelvic vein thrombosis.

Case 2. G.S. a male aged 68 was admitted to a medical ward on 5th May, 1949. Two days before admission he had developed acute pleuritic pain in the right chest. Clinical and radiological examination of the chest showed a small right pleural effusion without evidence of parenchymatous lung disease. Although the patient had not complained of it, there was also evidence of thrombo-phlebitis of the left leg. Blood count gave W.B.C. 5,000/cu.mm. with normal cell proportions - eosinophils 3%. Diagnostic aspiration of the pleural fluid gave the following findings:- Haemorrhagic fluid with thick clot; protein 5 Gms./100 mls.; cell count 1,200/cu.mm.; differential count - eosinophils 56%, neutrophils 20%, lymphocytes 20%, serosal cells 4%; ordinary culture sterile.

One week after admission he had a further attack of right pleuritic pain followed by haemoptysis. Further diagnostic aspiration of the pleural fluid again showed a haemorrhagic exudate; the cell content was now scanty and consisted of a few lymphocytes only. Treatment with anti-coagulants was instituted and subsequent progress was uneventful. Follow-up radiology showed no evidence of lung pathology. Although bronchial carcinoma was

suspected initially, the final diagnosis was recurrent pulmonary embolism with associated pleural effusion following thrombo-phlebitis of the leg veins

Case 3. G.M. a male aged 41 was admitted to a medical ward on 7th June, 1949. Two weeks previously he had suddenly become ill with shivering, weakness, anorexia and vomiting. One week later, while still confined to bed on sulphonamide therapy, he developed acute pleuritic pain in the right chest with slight cough and mucoid sputum; increasing dyspnoea caused his admission to hospital. Clinical and radiological examination of the chest showed a moderately large right pleural effusion without evidence of parenchymatous lung disease. Blood examination showed W.B.C. 5,400/cu.mm. with normal proportions - eosinophils 4%; B.S.R. 75 mms. in 1 hour (Westergren). Diagnostic aspiration of the fluid gave the following findings:- Clear serous fluid with thick clot; protein 5.78 Gms./100 mls.; cell count 1,300/cu.mm.; differential count - eosinophils 70%, neutrophils 5%, lymphocytes 15%, serosal cells 10%; ordinary culture - sterile; Lowenstein-Jensen culture - sterile.

His condition improved with remarkable rapidity; no fluid could be obtained on attempted diagnostic aspiration after one week. At no time in the ward did he have pyrexia or tachycardia. B.S.R. became normal in two weeks. Several specimens of sputum showed no growth of tubercle bacilli on Lowenstein-Jensen culture. Further, a Mantoux test (1:100) was negative and has remained so during follow-up for three years. Follow-up radiology of chest has confirmed the absence of parenchymatous lung disease.

No absolutely certain diagnosis could be made in this case. Striking features following admission to hospital were the transient nature of the effusion and the absence of toxæmic upset, both of which are unusual in post-primary tuberculous effusion, a diagnosis in any case excluded by the persisting negative Mantoux test. There was no clinical or radiological evidence of hydatid disease. Other serious diseases (e.g. tumour, reticulosis, periarteritis nodosa) were excluded by follow-up. It is probable that he began with a simple inflammatory lung condition, which, modified by sulphonamide therapy, resolved during the two weeks prior to his investigation in hospital, but in the meantime produced a sterile inflammatory effusion.

Case 4. Miss N.B. aged 17 developed a left pleural effusion following thoracotomy for closure of a patent ductus arteriosus on 9th December, 1949.

Diagnostic aspiration showed a heavily blood-stained fluid with thick clot; it contained 60% eosinophils and 40% serosal cells and was sterile on culture. Examination of the peripheral blood was not done. No doubt the origin of the effusion was partly traumatic and partly irritative from the presence of blood in the pleural cavity.

Case 5. A.M. aged 40 was admitted to a medical ward on 29th November, 1949. Six weeks before he had developed mild left renal colic associated with bladder pain on micturition. He was off work during the six weeks without special treatment from his family doctor. Three days before admission he developed another pain, this time typically pleuritic in type and situated over the left lower ribs posteriorly; there was also some cough with mucoid sputum, but no shivering or fever. Clinical and radiological examination of the chest revealed a small left pleural effusion without evidence of parenchymatous lung disease. Clinical examination of the genito-urinary tract was negative; urine contained no albumin, crystals or pus cells and was sterile on culture. Blood examination showed W.B.C. 6,200/cu.mm. with normal proportions - eosinophils 2%; B.S.R. 82 mms. in 1 hour (Westergren). Diagnostic aspiration of the pleural fluid gave the following findings:- Clear serous fluid with thin clot; cell count 1,100/cu.mm.; differential count - eosinophils 58%, neutrophils 8%, basophils 2%, lymphocytes 10%, serosal cells 22%; the serosal cells were notably large with prominent nuclei and showed a tendency to aggregate into clumps; ordinary culture - sterile; Lowenstein-Jensen culture - sterile.

During a stay of seven weeks in the ward he remained apyrexial with slight tachycardia (80-90/min.). B.S.R. remained elevated at 70 mms. in 1 hour. The pleural fluid absorbed very slowly; repeat diagnostic aspiration after one month showed no appreciable change in cytology from the original findings. There was no recurrence of urinary symptoms and complete urological investigation showed no abnormality of the urinary tract. Numerous specimens of sputum and a 24 hour specimen of urine were negative on culture for tubercle bacilli. Mantoux test (1:100) was positive.

He was discharged from hospital on 16th January, 1950. After a short spell of convalescence, the pleural fluid absorbed completely and B.S.R. fell rapidly to normal. During follow-up for $2\frac{1}{2}$ years he has remained extremely well and serial X-rays of chest have revealed nothing apart from residual pleural thickening at the site of the effusion.

As in Case 3, a certain diagnosis could not be made. Tuberculosis could not be excluded as a cause of the pleurisy with effusion, but the history of onset was not typical of tuberculosis. The unusual serosal cells in the fluid raised a suspicion of neoplasm, but follow-up has excluded this possibility. It is possible that he had a urinary infection prior to admission with spread of infection from the left kidney, where the original pain was maximal, through the perinephric tissues and diaphragm to the left pleural cavity; the indolent nature of the effusion with long continued elevation of B.S.R. is, however, somewhat against such a simple sterile inflammatory effusion.

Case 6. W.P. aged 27 was admitted to a medical ward on 13th December, 1949. Four weeks before admission, while sitting in a cinema, he developed sudden left pleuritic pain. On going home to bed he felt shivery and fevered. Some cough and mucoid sputum appeared the next day. His doctor kept him at rest in bed. For some months prior to his illness he had felt easily tired and had become thinner. Clinical and radiological examination of the chest showed a small left pleural effusion without evidence of parenchymatous lung disease, although on the X-ray both hilar shadows were abnormally prominent. Blood examination showed W.B.C. 7,400/cu.mm. with normal proportions - eosinophils 5%; B.S.R. 12 mms. in 1 hour (Westergren). Diagnostic aspiration of the fluid gave the following findings:- Clear serous fluid with thin clot; cell count 800/cu.mm.; differential count - eosinophils 76%; neutrophils 0%, basophils 1%, lymphocytes 20%, serosal cells 3%; ordinary culture - sterile; Lowenstein-Jensen culture - sterile. Numerous specimens of sputum were negative on culture for tubercle bacilli. Mantoux test (1:100) was positive.

He was in the ward for one week, during which temperature and pulse remained normal. He was then transferred to a convalescent hospital where further progress was satisfactory and he was discharged home on 11th April, 1950.

Unfortunately, on 6th May, 1950, left pleuritic pain recurred with formation of a further pleural effusion. B.S.R. was 12 mms. in 1 hour. Diagnostic aspiration as an out-patient gave the following findings:- Heavily blood-stained fluid with thick clot; cell count - not done; differential count - lymphocytes 75%, neutrophils 10%, eosinophils (disintegrating) 10%, serosal cells 5%; ordinary culture - sterile; Lowenstein-Jensen culture - sterile. The second pleurisy subsided

rapidly with rest in bed at home. He has remained well for two years and serial chest X-rays show slight residual pleural thickening.

Although no positive proof was forthcoming, the whole course of the illness in this case was highly suggestive of a tuberculous aetiology. It should be noted that the first diagnostic aspiration was performed four weeks after the initial pleurisy. It is of interest that the second pleurisy six months after the first gave a blood-stained effusion with reduction in eosinophil content from 76% to 10%.

Case 7. T.M. aged 32 was admitted to a medical ward on 4th July, 1950. His history was typical of lobar pneumonia. Clinical and radiological examination of the chest showed a right lower lobe consolidation with a small overlying right pleural effusion. His own doctor had already treated him with penicillin and sulphonamide. Blood examination showed W.B.C. 7,400/cu.mm. with normal proportions - eosinophils 2%; B.S.R. 58 mms. in one hour (Westergren). Diagnostic aspiration of the pleural fluid gave the following findings:- Clear serous effusion with thick clot; cell count 1,700/cu.mm.; differential count - eosinophils 82%, basophils 1%, neutrophils 0%, lymphocytes 13%, serosal cells 4%; ordinary culture - sterile; Lowenstein-Jensen culture - sterile. Bacteriological examination of sputum showed a mixture of organisms, but no tubercle bacilli. Progress in the ward was entirely satisfactory and X-ray of chest prior to discharge showed almost complete disappearance of the consolidation and fluid. He has remained well over a two year follow-up.

The final diagnosis was right lower lobe pneumonia with a sterile syn-pneumonic pleural effusion.

Case 8. Mrs. A.G. aged 51 was admitted to a medical ward on 27th July, 1950. Four weeks before admission she had developed acute pleuritic pain in the right chest followed by pain and swelling in the left leg. Clinical examination revealed an extensive thrombo-phlebitis of the left leg and a small right pleural effusion. Radiological examination of the chest confirmed the presence of a right pleural effusion with some underlying opacity in the right lower lobe. Blood examination showed W.B.C. 9,200/cu.mm. with normal proportions - eosinophils 4%. Diagnostic aspiration of the pleural fluid gave the following findings:- Slightly cloudy fluid (not blood-stained); protein 8 Gms/100 mls.; cell count - not done; differential count - eosinophils 55%, neutrophils 10%, lymphocytes 35%; ordinary

culture - sterile; Lowenstein-Jensen culture - sterile. The sputum was also negative on culture for tubercle bacilli. While in the ward she was afebrile with a normal pulse rate. The thrombophlebitis subsided with anti-coagulant therapy and the pleural effusion absorbed. She was discharged after one month. Six months later she had no abnormal symptoms or signs and chest X-ray showed only residual pleural thickening in the right costo-phrenic angle. The final diagnosis was pulmonary embolism with associated pleural effusion following thrombophlebitis of the leg veins.

Comments on the Eight Cases.

In five (nos. 1, 2, 4, 7 and 8) of the eight cases, the aetiology of the pleural effusion was definitely established, viz. pulmonary infarction (3 cases), lobar pneumonia (1 case) and post-thoracotomy (1 case). In the remaining three cases, the aetiology could not be established; in one (case 3) tuberculosis could be excluded on the basis of a persistently negative Mantoux test, and the course of the illness suggested a simple inflammatory condition; in another (case 6) tuberculosis, although not proved, seemed the most probable aetiological factor; in the third (case 5), the evidence was equally balanced between a simple inflammatory and tuberculous aetiology. In no case was there evidence either at the time or on subsequent follow-up of "eosinophilic lung", periarteritis nodosa, blood dyscrasia, reticulosis, neoplasm, parasitic infection or "allergic diathesis".

All of the fluids were sterile on ordinary

culture. Two (case 2 - pulmonary infarction and case 4 - post-thoracotomy) were heavily blood-stained on initial aspiration. The remaining six (nos. 1, 3, 5, 6, 7 and 8) were clear and serous or only slightly cloudy. The clot formation and/or protein estimation indicated that in each case the fluid was an exudate rather than a transudate, while the differential cell count revealed the striking preponderance of eosinophils; in three cases (nos. 5, 6 and 7) there was also an appreciable number of basophils. Repeat diagnostic aspiration was performed after an interval of from one to four weeks in three cases: in case 1 (pulmonary infarction) and case 5 (diagnosis uncertain), the fluid was macroscopically and cytologically unchanged; in case 2 (pulmonary infarction) the eosinophilic exudate had changed to a lymphocytic exudate. In another case (case 6 - probably tuberculous), pleurisy with effusion recurred after an interval of six months; the fluid, initially clear and serous, was now found to be blood-stained, and the content of eosinophils had fallen from 76% to 10%.

It must be emphasised that in seven of the eight cases so investigated there was no eosinophilia or even leucocytosis in the peripheral blood either during the formation or absorption of the eosinophilic pleural fluid.

Discussion.

From the practical point of view the main interest of eosinophilic pleural effusion lies in the question of whether or not it has any diagnostic or prognostic significance in the individual case. It is proposed to discuss this in relation to various possible aetiological factors:-

(a) Pneumonia. One case of the present series developed a sterile eosinophilic pleural effusion during the course of a lower lobe pneumonia. Bayne-Jones (1916) describes a similar case in detail and refers to eight others within his experience. Close (1946) refers to two cases who gave histories of "recurrent pneumonia" over a period of five years. "Pulmonary congestion" - probably pneumonia - is given as a cause by Faure-Beaulieu (1938) - 1 case - and Mosny and Portocalis (1913) - 2 cases. Ellis (1945) states that "the presence of eosinophils in the uncommon clear effusions following pneumonia indicates the probability that the fluid will not become purulent", a point previously noted by Trail (1943).

(b) Pulmonary Infarction. Three cases of the present series developed eosinophilic pleural effusion following pulmonary infarction. There is no previous reference to this occurrence in the literature.

(c) Trauma. One case of the present series developed

a sterile blood-stained eosinophilic pleural effusion following thoracotomy for the closure of a patent ductus arteriosus. Possibly this is an example of operative trauma and is analagous to the pleural eosinophilia described by Gregoire and Courcoux (1919) in relation to traumatic haemothorax.

(d) Tuberculosis. Ellis (1945) states that "the presence of eosinophils in any number is usually evidence against the infection being tuberculous". On the other hand, Gill (1940) describes a case of abdominal and pleural tuberculosis proved by necropsy in which the pleural fluid contained 80% eosinophils; he also refers to 3 other tuberculous cases described in the literature and draws attention to the fact that eosinophils may be found in effusions complicating artificial pneumothorax therapy for pulmonary tuberculosis; in the latter, according to Pavie, Lefèvre and Rossignol (1937), who produced pleural eosinophilia in a healthy rabbit by inducing a pneumothorax, trauma to the pleura may be a factor. MacMurray, Katz and Zimmerman (1950) state that pleural eosinophilia may occur in tuberculous effusion, but that it never occurs early in the course of the disease; by this statement they presumably mean that it does not occur in the common type of post-primary tuberculous effusion.

During the collection of the present series of cases, pleural fluid from 163 cases was examined cytologically. Of the 163 cases, 97 were finally regarded as tuberculous or probably tuberculous in origin; of those 97 cases, only one - an unproved case - showed pleural eosinophilia. In one further case showing pleural eosinophilia, tuberculosis was a possible but not a probable diagnosis. It is therefore concluded both from this study and from the review of the literature that pleural eosinophilia is a most uncommon finding in tuberculous pleural effusion.

(e) "Eosinophilic Lung". Nagel (1941) describes a case of Loeffler's Syndrome complicated by a massive pleural effusion in which blood eosinophilia reached 9% and fluid eosinophilia 83%. Baumann (1944) describes a similar case presenting with chest symptoms in which both sputum and pleural fluid contained a high proportion of eosinophils; the W.B.C. count in the peripheral blood was 14,500/cumm. with 25% eosinophils; later the patient passed ova of ascaris lumbricoides in the stool. Harkavy (1941), writing on vascular allergy, refers to 8 cases of asthma associated with pulmonary infiltrations and blood eosinophilia; of the 8 cases, 6 had effusion into one or both pleural cavities, the eosinophil content varying from 85% to 100%.

Crofton, Livingstone, Oswald and Roberts (1952) believe that pleural effusion containing a high proportion of eosinophils may occur in any of the subgroups of "pulmonary eosinophilia" - e.g. Loeffler's Syndrome, Weingarten's Syndrome, periarteritis nodosa; they further point out that on occasion the effusion may obscure an underlying pulmonary lesion in the chest X-ray, thus causing the case to present as one of primary eosinophilic pleural effusion.

Only if eosinophilia is detected in the peripheral blood can a diagnosis of "pulmonary eosinophilia" be entertained. In the present series of cases there was none with blood eosinophilia and none with suggestive radiological changes in the lungs. From the practical point of view it should be kept in mind that "pulmonary eosinophilia" is not only uncommon in Great Britain, but it is also uncommon for it to cause a pleural effusion.

(f) Hydatid Disease. Ellis (1945) states that "a combination of true eosinophilia in pleural fluid and peripheral blood is usually presumptive evidence of hydatid disease".

(g) Miscellaneous Conditions. Isolated cases of pleural eosinophilia have been described in association with Hodgkin's Disease - MacMurray, Katz and Zimmerman (1950), generalised dermatitis - Close (1946), bronchial carcinoma - Bernard, Marie and Anchel (1931), "hay fever diathesis" - MacMurray, Katz

and Zimmerman (1950), and amoebic abscess of the lung - de Lavergne, Abel and Debenetti (1930). References to Hodgkin's Disease, generalised dermatitis and "hay fever diathesis" are not surprising in view of the known association of eosinophilia with those conditions. It is of interest that the reference to bronchial carcinoma is the only one in the literature associating pleural eosinophilia with tumour. Cases in which a final diagnosis could not be made are also mentioned by Crofton, Livingstone, Oswald and Roberts (1952), Reinikainen (1947) and Punch and Close (1938).

The Mechanism of Production of Pleural Eosinophilia.

Although in some cases - e.g. "pulmonary eosinophilia", hydatid disease - pleural eosinophilia may be part of a generalised disturbance, the absence, in the present series of cases, of blood eosinophilia, suggests that the cause is often localised to the pleural cavity. It is tempting to assume with Bayne-Jones (1916) the presence of an eosinotactic substance in the pleural exudate. If such a substance exists, it must do so as a largely non-specific phenomenon common to a variety of pathological processes in the pleural cavity. It has been pointed out by Crofton, Livingstone, Oswald and Roberts (1952) and MacMurray, Katz and Zimmerman

(1950) that approximately two-thirds of the cases described in the literature have been associated with haemorrhagic pleural fluid. Haemorrhage, however, cannot be the only factor, since only 2 of the 8 cases in the present series had blood-stained fluid initially. Furthermore, numerous cases of haemorrhagic fluid without associated pleural eosinophilia have been observed in malignant disease. In case 6 with an initially clear fluid, the development of haemorrhagic fluid was associated with a striking fall in the eosinophil content. The association with traumatic haemothorax - Gregoire and Courcoux (1919), pleural fluid complicating artificial pneumothorax - Pavie, Lefèvre and Rossignol (1937), thoracotomy and pulmonary infarction suggests that trauma to the pleura, possibly associated with haemorrhage, may be a factor in some cases. Occasionally the eosinophilic exudate has in the course of time given way to a lymphocytic exudate - Harvier and Mallarmé (1937); case 2 of the present series. This may have no significance, but it may also suggest that lymphocytes and eosinophils have an obscure inter-relationship; in this connection, Blalock, Robinson, Cunningham and Gray (1937) have observed that complete lymphatic blockage in the dog leads to disappearance in the blood not only of lymphocytes, but also of eosinophils. It is clear

that the immediate causation of pleural eosinophilia, although a fruitful subject for speculation, is ill-understood and requires further investigation.

Another obscure problem is the occasional presence of a small number of basophils along with the eosinophils. This was observed in 3 cases of the present series and has previously been reported by Mosny and Portocalis (1913) and Bayne-Jones (1916).

Conclusion:

It is now convenient to refer again to the main analysis of the Leishman film investigation of 146 fluids, so that to it can be added information derived from this sub-section. From the diagnostic point of view in the individual case of pleural eosinophilia certain tentative suggestions can be made. If blood eosinophilia co-exists with the pleural eosinophilia, the patient should be investigated for the presence of hydatid disease, "pulmonary eosinophilia" (Loeffler's Syndrome, Weingarten's Syndrome, periarteritis nodosa) and possibly Hodgkin's Disease. If there is no blood eosinophilia, pulmonary infarction, trauma to the pleura and pneumonia should be considered in diagnosis. (Although, for convenience, two groups of conditions depending on the presence or absence of blood eosinophilia have been given it is not suggested that the

distinction is absolute). Malignant disease is an improbable diagnosis in the presence of pleural eosinophilia. Tuberculosis cannot be excluded as a cause, but the available evidence suggests that it should not be readily diagnosed unless other strong evidence is forthcoming. On occasions a definite diagnosis may not be established. Finally, too much significance should not be attached to the presence of blood in the fluid.

From the prognostic point of view, little can be said since so much depends on the ultimate diagnosis. Ellis (1945) and Trail (1943) state that in eosinophilic effusion due to lobar pneumonia, empyema is most unlikely to develop. MacMurray, Katz and Zimmerman (1950) state that most eosinophilic effusions are transient in nature and pursue a benign course. In the present series of cases, all certainly pursued a relatively benign course, but only 2 could be called transient.

Addendum.

Since the sub-section on pleural eosinophilia was written, details of a further case, not personally observed, have been supplied to the author through the kindness of Dr. Hiddlestone of the Edinburgh City Hospital:-

Mrs. C.M. aged 23 had a right artificial

pneumothorax induced on 3.9.52 for the treatment of pulmonary tuberculosis involving the right upper lobe. Selective collapse was prevented by numerous pleural adhesions which were sectioned at thoracoscopy by Mr. A. Logan on 17.10.52. Section was complete, but a small right pleural effusion developed without constitutional upset. Diagnostic aspiration showed a clear fluid with total white cell count 2,800 per cu.mm., and eosinophils 41%, neutrophils 31%, lymphocytes 25% and serosal cells 3%. Blood examination showed a white cell count of 9,600 per cu.mm., with only 1% eosinophils. There was no personal or family history of asthma or other allergic condition. An intradermal injection of procaine from the same bottle used for the chest aspiration provoked no sensitivity reaction. The effusion rapidly absorbed. In the opinion of those in charge of the patient the effusion was traumatic rather than tuberculous in origin. From the evidence available, the author is in agreement with this opinion.

ILLUSTRATIVE PHOTOMICROGRAPHS OF LEISHMAN
FILM INVESTIGATION

Figures 1 to 6 illustrate some of the cytological pictures observed in post-primary tuberculous fluids.

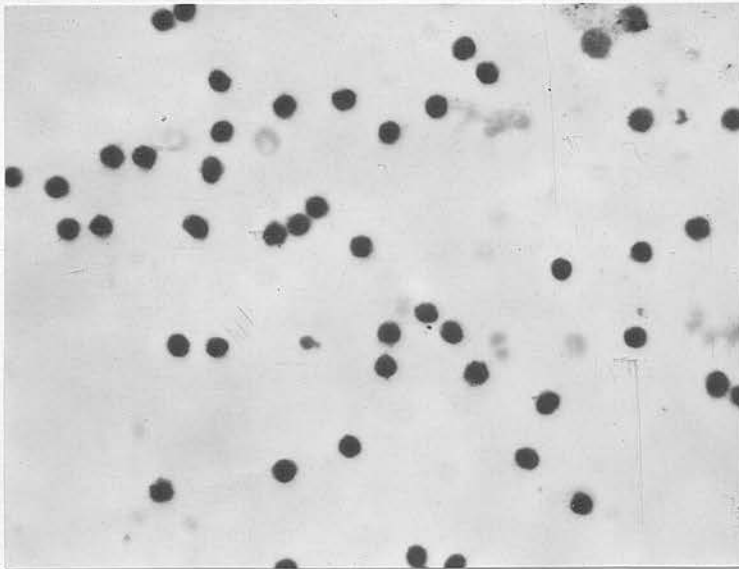


Fig. 1 X 600

Primary Tuberculosis

Lymphocytes 100%.

Although this is the typical picture of tuberculosis, a similar picture is occasionally observed in simple inflammation and in neoplasm.

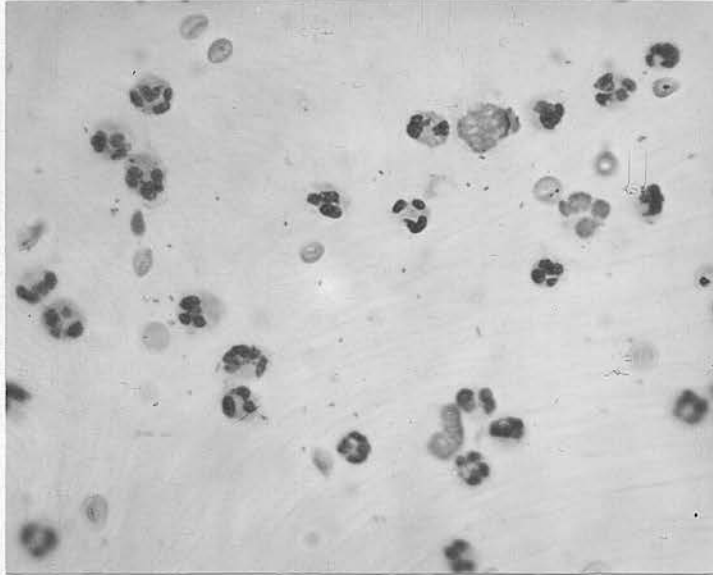


Fig. 2 X 600

Primary Tuberculosis

Lymphocytes	1%.
Polymorphs	98%
Serosal Cells	1%.

This is a rare but important finding in tuberculosis. Simple inflammation is closely simulated. In this particular case, the fluid did not become a tuberculous empyema, but the possibility of this development should be kept in mind.

Figures 3, 4 and 5 illustrate the changing cytology over a period of time in an initially puzzling case of post-primary tuberculous effusion. This problem has been discussed in detail in the text.

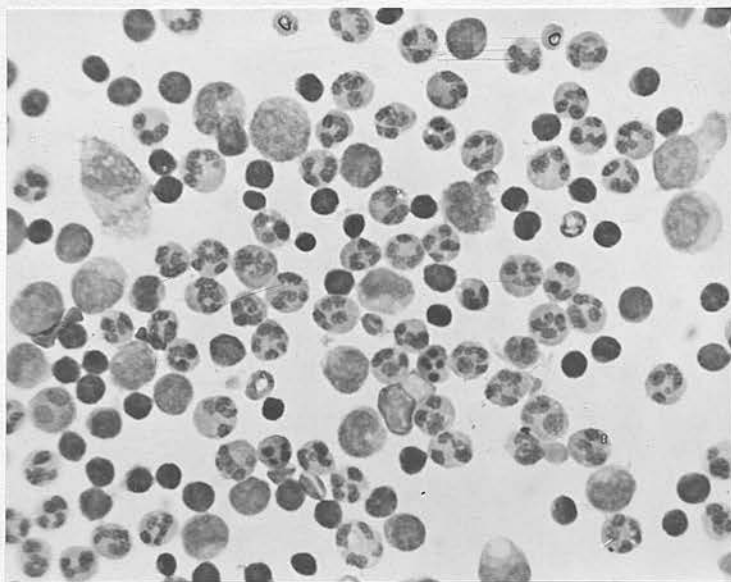


Fig. 3 X 600

Primary Tuberculosis

8th Oct. 1951 - initial aspiration:

Lymphocytes	36%.
Polymorphs	52%.
Serosal Cells	12%.

Simple inflammation seemed probable at this time.

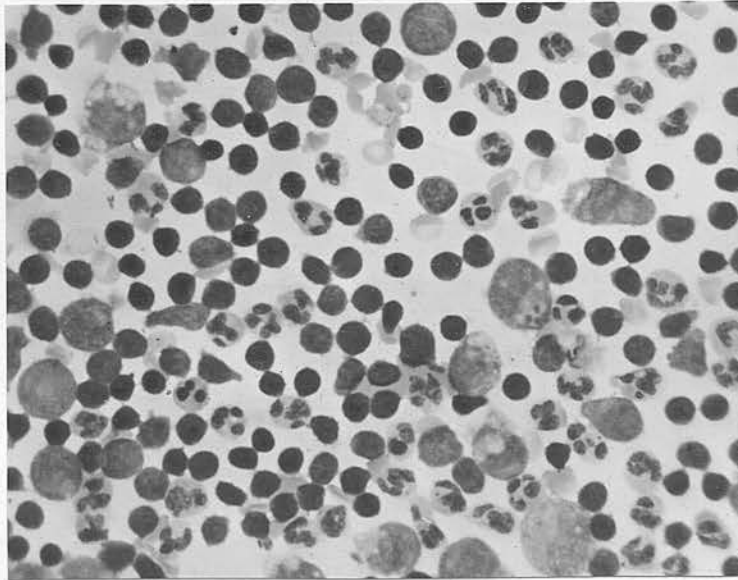


Fig. 4 X 600

Primary Tuberculosis
(same case as Fig.3)

17th Oct.1951 - second aspiration:

Lymphocytes	66%.
Polymorphs	26%.
Serosal Cells	8%.

The cytological picture was now more suggestive
of tuberculosis.

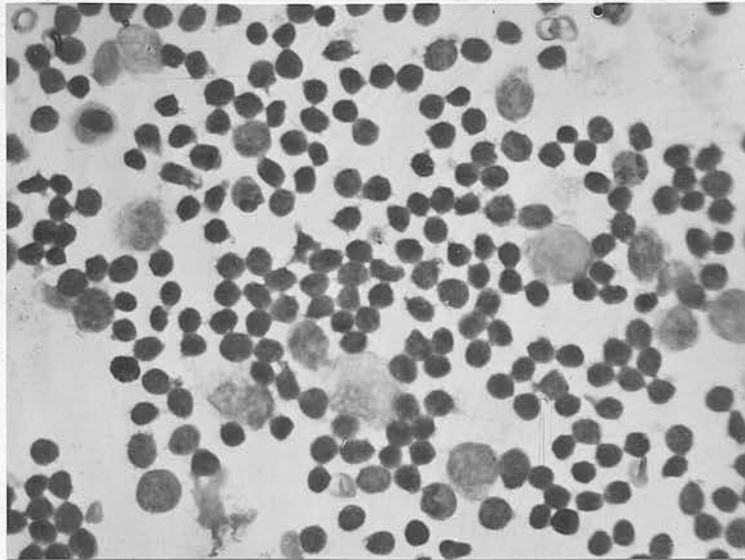


Fig. 5 X 600

Primary Tuberculosis
(Same case as Figs. 3 and 4)

9th Nov. 1951 - third aspiration:

Lymphocytes	97%.
Polymorphs	1%.
Serosal Cells	2%.

In the presence of increasing effusion, the cytological picture was now considered to indicate tuberculosis.

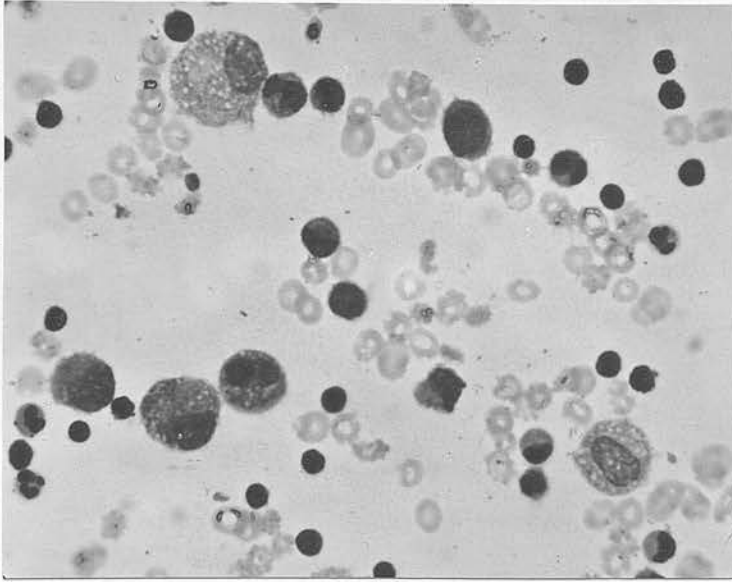


Fig. 6 X 600

Primary Tuberculosis

Lymphocytes	76%.
Polymorphs	9%.
Serosal Cells	15%.

From the diagnostic point of view, this is a troublesome picture. A percentage of serosal cells of this order is common to tuberculosis, neoplasm, transudate and pulmonary infarction.

For comparison with Figure 6, Figure 7 is that of an effusion secondary to pulmonary infarction.

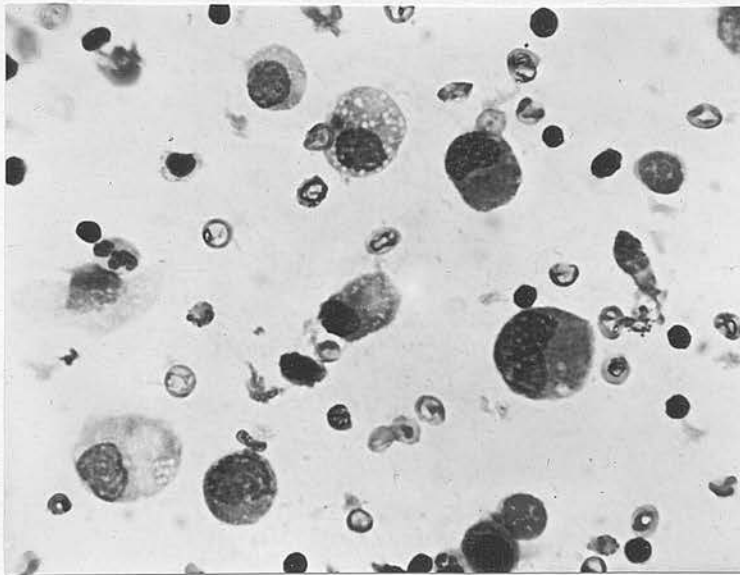


Fig. 7 X 600

Pulmonary Infarction

Lymphocytes	64%.
Polymorphs	4%.
Serosal Cells	32%.

Although the percentage of serosal cells is higher than in Figure 6, the difference is not significant and the picture is essentially the same.

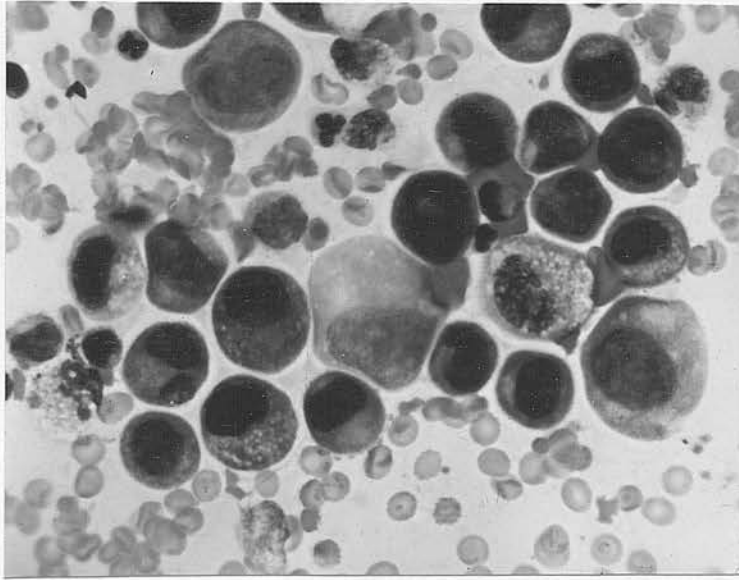


Fig. 8 X 600

Neoplasm - Bronchial Carcinoma

Lymphocytes	1%.
Polymorphs	1%.
Serosal Cells	98%.

This picture is probably diagnostic of neoplasm. Some of the cells illustrated may be actual neoplastic cells, but, with Leishman's stain, it is impossible to be certain. In the differential count, it is convenient to include all such cells as "serosal cells".

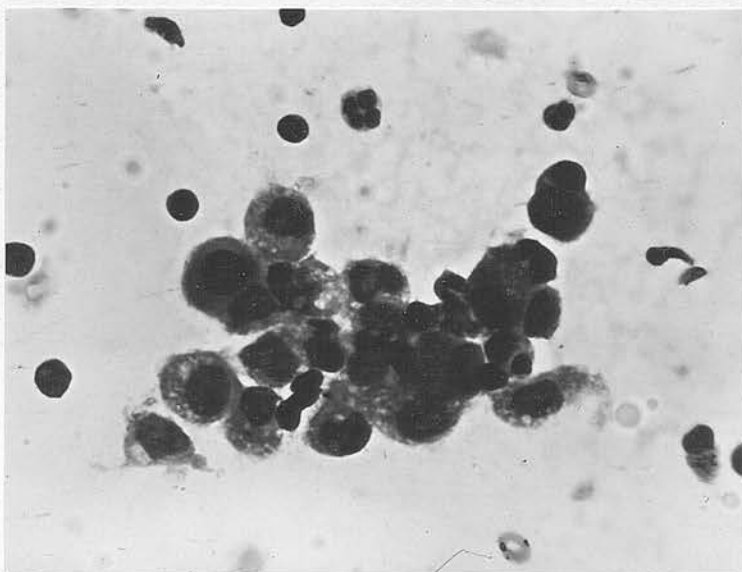


Fig. 9 X 600

Neoplasm - Secondaries from Gastric Carcinoma

Lymphocytes	29%.
Polymorphs	1%.
Serosal Cells	70%.

This picture is essentially the same as Figure 8. The cells tend to occur in clusters, making differential counting difficult. To overcome this difficulty, the counting should be done on a very thin film in which the clusters become broken up. Clusters are not confined to neoplastic fluids (see Figure 12).

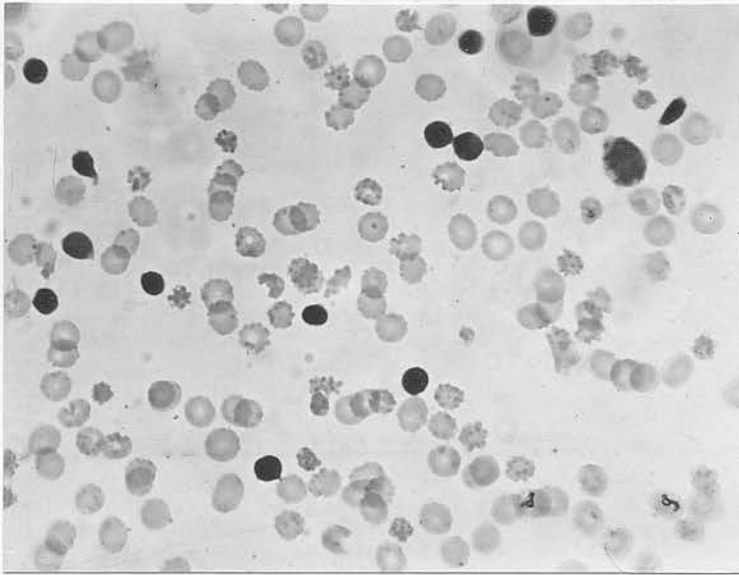


Fig. 10 X 600

Neoplasm - Bronchial Carcinoma

16th Jan. 1951 - initial aspiration:

Lymphocytes	92%.
Polymorphs	0%.
Serosal Cells	8%.

This is the non-specific lymphocytic picture of neoplasm. The fluid was haemorrhagic - note large number of red blood cells - and actually contained very few white cells. A second aspiration was done 15 days later (see Figure 11).

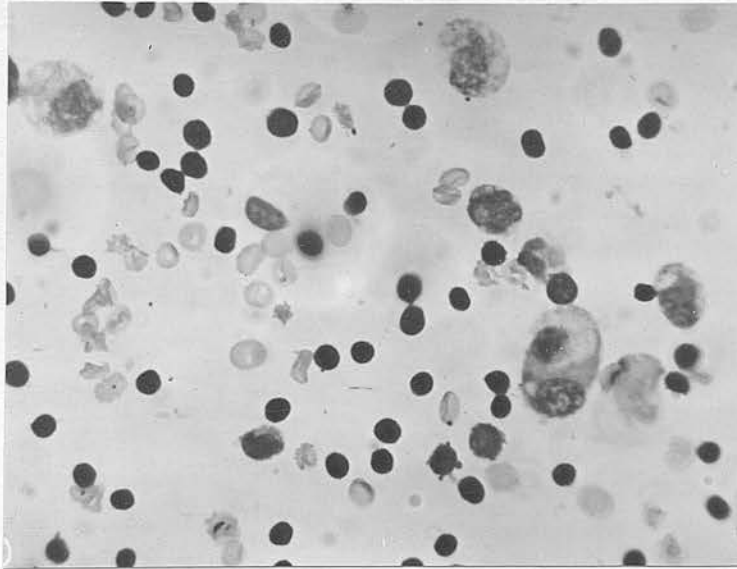


Fig. 11 X 600

Neoplasm
(same case as Fig.10)

31st Jan.1951 - second aspiration:

Lymphocytes	91%.
Polymorphs	0%.
Serosal Cells	9%.

The number of white cells has now increased (not due to a thicker film), but, as is the general rule in this type of fluid, no change in proportions has occurred.

In a cardiac transudate, the cytological picture tends to resemble that of neoplasm, although the serosal cell count is lower.

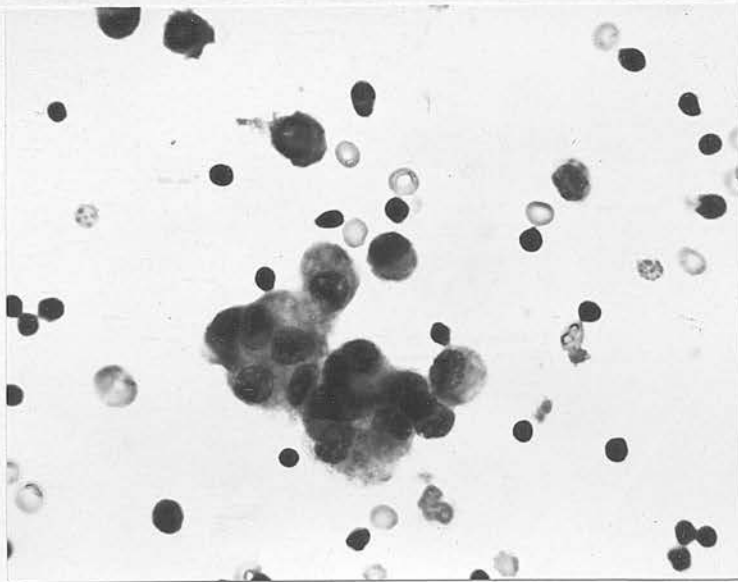


Fig. 12 X 600

Cardiac Transudate

Lymphocytes	40%.
Polymorphs	0%.
Serosal Cells	60%.

The general resemblance of this picture to that of Figure 9 should be noted.

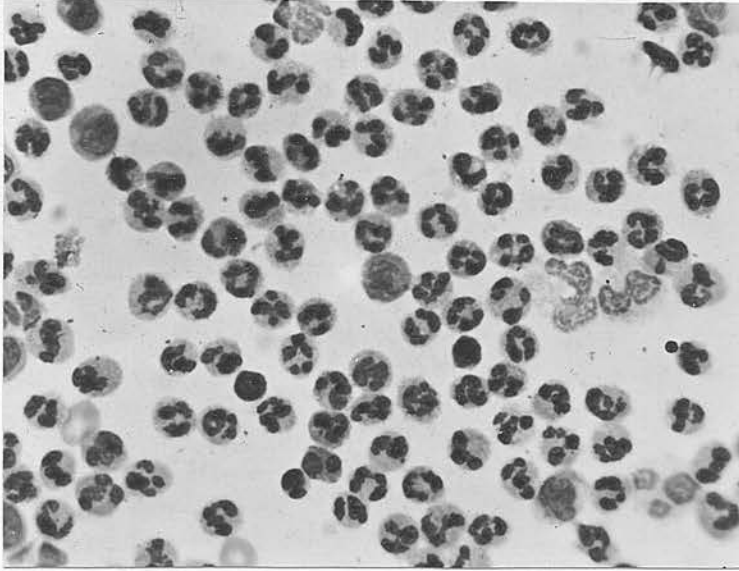


Fig. 13 X 600

Simple Inflammation

Lymphocytes	1%.
Polymorphs	97%.
Serosal Cells	2%.

This is the typical, but not invariable, picture of simple inflammation. It can also occur in tuberculosis (see Figure 2). The fluid in this case was serous.



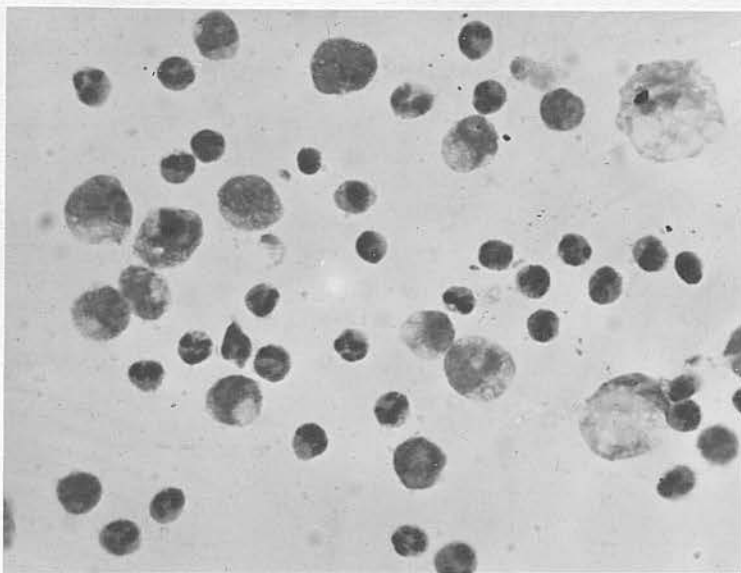


Fig. 14 X 600

Simple Inflammation - Subphrenic Abscess

Lymphocytes	2%.
Polymorphs	58%.
Serosal Cells	40%.

This case has been referred to in the text.

The combination of polymorphs and serosal cells is most unusual and may be typical of fluid secondary to subphrenic abscess.

The effect of intrapleural medication with P.A.S. (para-amino-salicylic acid) is illustrated in Figures 15 and 16.

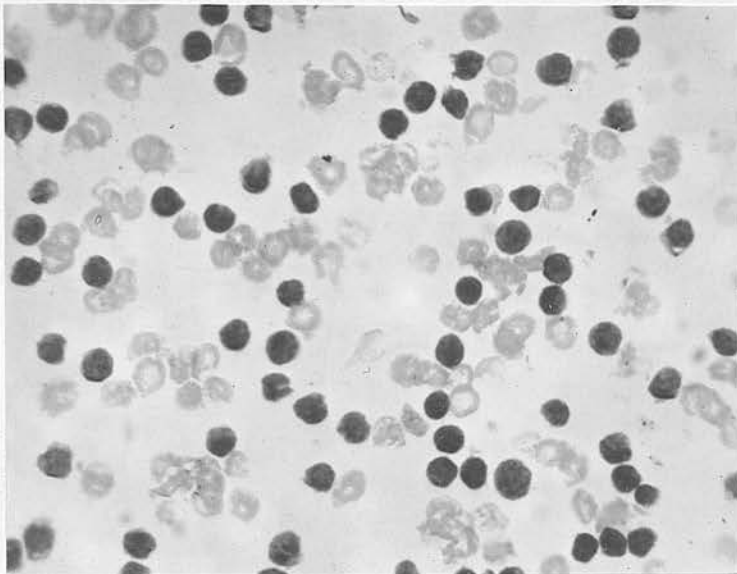


Fig. 15 X 600

Primary Tuberculosis

Lymphocytes	96%.
Polymorphs	1%.
Serosal Cells	3%.

Aspiration performed immediately prior to intrapleural P.A.S.

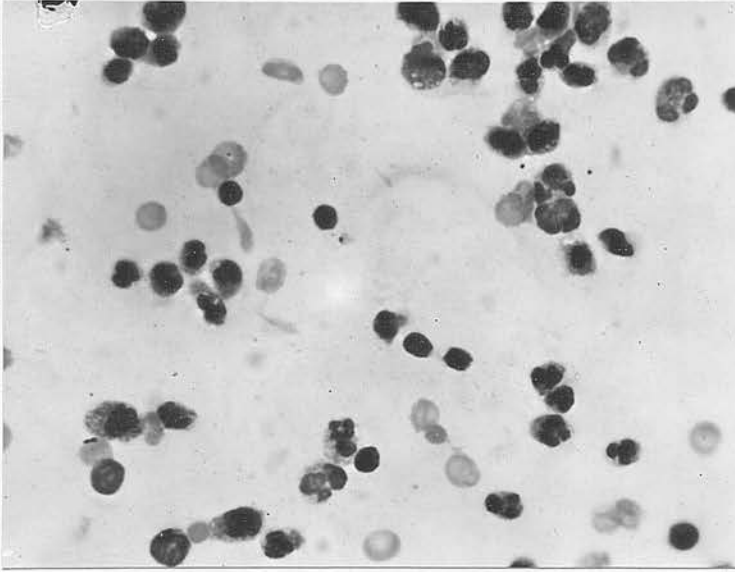


Fig. 16 X 600

Primary Tuberculosis
(Same case as Fig. 15)

Lymphocytes	51%.
Polymorphs	49%.
Serosal Cells	0%.

Aspiration performed 48 hours after intra-pleural P.A.S. (2 Gms.). The possible significance of this change in cytology is discussed in the text.

Illustrations of the Leishman film series conclude with representative examples of pleural eosinophilia.

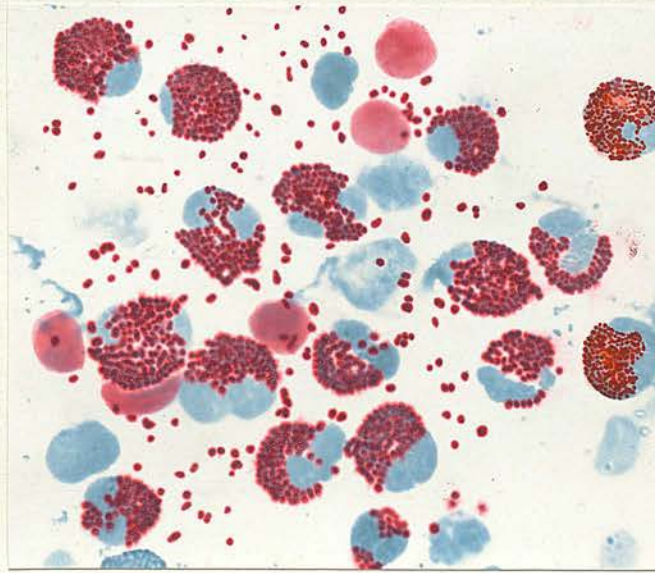


Fig. 17 X 850

Simple Inflammation - Syn-Pneumonic Effusion

Lymphocytes	13%.
Eosinophils	82%.
Neutrophils	0%.
Basophils	1%.
Serosal Cells	4%.

Three red blood cells are also seen in the field. The eosinophilic granules are typical, but perhaps more important in the recognition of the eosinophil cell with Leishman's stain, is the bilobed nucleus (even neutrophil granules may stain a little pink). The eosinophils are tending to disintegrate.

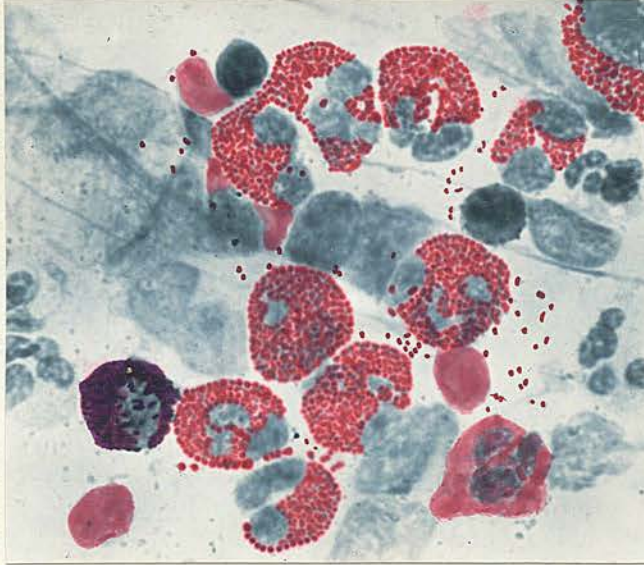


Fig. 18 X 1100

Undiagnosed - ? Simple Inflammation

Lymphocytes	10%.
Eosinophils	58%.
Neutrophils	8%.
Basophils	2%.
Serosal Cells	22%.

A basophil and some serosal cells are included in the field.

CYTOLOGICAL INVESTIGATION OF PLEURAL FLUID
(continued)

B. Search for Malignant Cells.

In contrast to the simplicity of recognising lymphocytes, neutrophils, eosinophils and basophils in pleural fluid, the identification of malignant cells is a problem which has long taxed the skill of pathologists and, be it said, the faith of clinicians. As far as the pathologist is concerned, the problem is by no means one of modern times; as long ago as 1895, Rieder stated that "it is understood that the finding of numerous polymorphous unequal large cells, especially when they have vacuoles and lie in clumps, speaks more for neoplastic than for mesothelial (serosal) cells, but the diversity of form of mesothelial cells in inflammatory processes in serous effusions is misleading". The difficulty encountered by Rieder is as real today as it was in 1895; indeed the Leishman film investigation already described proved to the author, after a careful study, that it is impossible to differentiate malignant cells from serosal cells with that particular technique. Since a Leishman film is the only method by which the clinician can conveniently study cytology in his own side-room, it is clear that he must rely on the pathologist, who can employ more complicated methods,

for the detection of malignant cells. This being so, it seemed desirable to undertake an investigation designed to test reliability of the pathologist in this respect.

The Nature of the Investigation.

1. The permission and co-operation of Dr. R.F. Ogilvie, Senior Pathologist to the Royal Infirmary of Edinburgh, were sought and obtained.

2. The fluids, constituting a series for the investigation, were simply all those sent to the Pathology Department, Royal Infirmary of Edinburgh, for examination for malignant cells during 1949, 1950 and the early part of 1951. Fluids were received from all the medical and some of the surgical charges during that period, although the numbers from each charge varied according to the enthusiasm of the Physician for this method of examination. No attempt was made to solicit the sending of extra fluids; indeed the Physicians were unaware that the investigation was going on. The number of fluids received for examination was 111. Some of those were repeat examinations, the total number of patients being 90.

3. Each fluid, consisting of a clotted specimen in a test tube, was prepared by the technical staff for cytological examination:

(a) A smear was made from the centrifuged deposit and stained with haematoxylin and eosin.

(b) A paraffin section was cut from a block in which the remainder of the centrifuged deposit had been placed; the section was also stained with haematoxylin and eosin.

4. Each cytological examination was made by the Senior Pathologist or his deputy; the report was sent to the clinician concerned.

5. It was now the duty of the author to check the accuracy of the Pathologist's report. This was done with the co-operation of the clinician in charge of each patient concerned. Clinical, radiological and, when appropriate, bronchoscopic, biopsy and autopsy evidence was surveyed. In the case of a surviving patient, a complete follow-up investigation was undertaken. In 87 of the 90 patients, a certain or reasonably certain diagnosis, not based on the cytological examination, was established.

Analysis of Malignant Cell Investigation:

TABLE 7 /

TABLE 7Age Distribution of 90 Patients Investigated

Age in Years	No. of Patients
10 - 19	3
20 - 29	5
30 - 39	6
40 - 49	12
50 - 59	22
60 - 69	27
70 - 79	14
80 - 89	1
Total	90

This table hardly requires comment. Although, in a general hospital, most patients with pleural effusion are in younger age groups, it is only in the older age groups that search for malignant cells is generally requested. It is probable that in the 8 patients under the age of 30 the diagnosis of malignancy was not entertained very seriously.

TABLE 8 /

TABLE 8Ultimate Diagnosis of 90 Patients Investigated

Diagnosis	No. of Patients	
Bronchial Carcinoma	27	} 41
Other Carcinoma or Sarcoma (1)	14	
Transudate - Cardiac, Renal	17	
Simple Inflammation	16	
Post-Primary Tuberculosis	7	
Pulmonary Infarction	5	
Meig's Syndrome	1	
Undiagnosed	3	
Total	90	

Note (1). This group included carcinoma of breast, pancreas, ovary, caecum, kidney, ureter, gall-bladder, rectum and parotid gland; seminoma of testis; lymphosarcoma of mediastinum.

By good fortune the 90 patients consisted of 41 malignant and 46 non-malignant cases (3 undiagnosed), thus giving approximately equal groups for comparison.

TABLE 9 /

TABLE 9Report by Pathologist on 90 Cases (111 Fluids)

Report	No. of Cases
Malignant Cells Present (1)	37
Malignant Cells Absent (1)	53
	90

Note (1). On one or more occasions.

TABLE 10Report by Pathologist in Relation
to Ultimate Diagnosis

Diagnosis	No. of Cases	Report by Pathologist	
		Malignant Cells Present	Malignant Cells Absent
Bronchial Carcinoma	27	17	10
Other Carcinoma	14	6	8
Transudate	17	8	9
Simple Inflamm.	16	2	14
Tuberculosis	7	0	7
Pulm. Infarct.	5	3	2
Meig's Syndrome	1	0	1
Undiagnosed	3	1	2
	90	37	53

Comments on Table 10:

It is immediately obvious that of 46 non-malignant fluids, 13 were said to contain malignant

cells - i.e. 13 proved to be "false positives". This finding must not be taken as a reflection on the ability of a group of Pathologists who are well known in Edinburgh for a high standard of diagnostic skill in all fields of their work; rather it must be taken as an indication of the extreme difficulty which exists in the identification of malignant cells. If the number of "false positives" seems high in relation to the claims of other Pathologists, it should be remembered that no investigation reported in the literature has been conducted in such a severely objective manner as the present one. Foot (1937) had no false positive report in a series of 85 pleural fluids, but, of the 85, 82 were from malignant cases, and hence there was little chance of obtaining a false positive. Bamforth (1946) referred to 26 fluids positive for malignant cells, but in at least 11 of the 26, no further information could be obtained about the patient. Zemansky (1928) reported only 10 positives in a small series of 35 fluids; of the 10, 1 could not be verified as a case of malignant disease. Chapman and Whalen (1947) reported 102 positives from a very large series of 833 fluids from 666 patients; they indicated that of 50 positives, 3 proved to be "false", no mention being made of the other 52 positives.

The table also shows that of 41 malignant fluids,

18 were said to contain no malignant cells - i.e. 18 proved to be "false negatives". Needless to say, this finding, in contrast to that of the "false positives", is unimportant; no clinician would exclude malignant disease on a negative report; no pathologist would be expected to find malignant cells in every fluid due to malignant disease.

Lastly it is of interest to note the type of case in which the dangerous error of a "false positive" tended to occur. Tuberculosis - 0 of 7 and simple inflammation - 2 of 16 seemed relatively immune. Transudate - 8 of 17 and pulmonary infarction - 3 of 5 provided the main sources of error. This observation is in keeping with the known presence of numerous serosal cells in transudates and infarction fluids, and the known difficulty of differentiating serosal cells from malignant cells.

Retrospective Study of Malignant Cell Series.

The next step in the investigation was to re-examine the smears and sections in retrospect with the ultimate diagnosis in each case available so that a scheme for the future avoidance of errors could be worked out. The re-examination was carried out by the author, who is entirely responsible for any opinions expressed, but who nevertheless wishes to thank Dr. R. F. Ogilvie and Professor A.M. Drennan of the Department of Pathology, University of Edinburgh,

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for advice freely given on the numerous points of difficulty which arose.

The results of re-examination are best presented in the first instance with illustrative photomicrographs and appropriate comments.

The first point for illustration and comment is the difference in appearance of cells on a haematoxylin and eosin smear on the one hand and a haematoxylin and eosin paraffin section on the other.

Rosenthal (1950) prefers a smear for the following reasons:-

- i. The nucleoli are better seen.
- ii. Cornification in a squamous carcinoma is more obvious.
- iii. Shrinkage of cell cytoplasm does not occur so that a truer appreciation of the nucleocytoplasmic ratio is obtained.
- iv. False hyperchromatism of nuclei due to shrinkage is obviated.

Bamforth (1946) also prefers a smear because "the cells are not so shrunken and give a more faithful representation of the real morphology; the appearances are more accurate and detail more intimate". On the other hand, Foot (1937), Zemansky (1928) and Chapman and Whalen (1947), without giving reasons, prefer a paraffin section. Mandlebaum (1917), who was the first to examine pleural fluids on a significantly large scale, also used a paraffin section technique.

That shrinkage of cells takes place during the processing of a paraffin section there is no doubt. Figures 19 and 20 are photomicrographs of the same magnification of the smear and section from a simple inflammatory fluid containing mainly polymorphs. The shrinkage is obvious. As might be expected, lymphocytes, because of their lesser quantity of cytoplasm, do not shrink so much. Indeed, Figures 21 and 22 from the smear and section of a tuberculous fluid containing mainly lymphocytes show a barely appreciable difference.

A more significant point is observed in Figures 23 and 24 from the smear and section of a transudate containing mainly serosal cells. Although some shrinkage of the cells has occurred in the section, the over-all picture has a degree of clarity and definition completely lacking in the smear. This advantage of the section was demonstrated consistently in all the fluids examined, and the author has no doubt that with haematoxylin and eosin stain at least, the section should be used to the exclusion of the smear. As will be demonstrated with subsequent photomicrographs, which are all of sections, the disadvantages cited by Rosenthal and Bamforth - *vide supra* - are not particularly troublesome. A last, but not unimportant, factor governing the choice of the section rather than the smear,

is that a pathologist, as opposed to a special cytologist, is accustomed to looking at paraffin sections in the course of his routine work, and hence to him the shrunken cell is a normal phenomenon.

(Figures 19 - 24 on the following pages.)

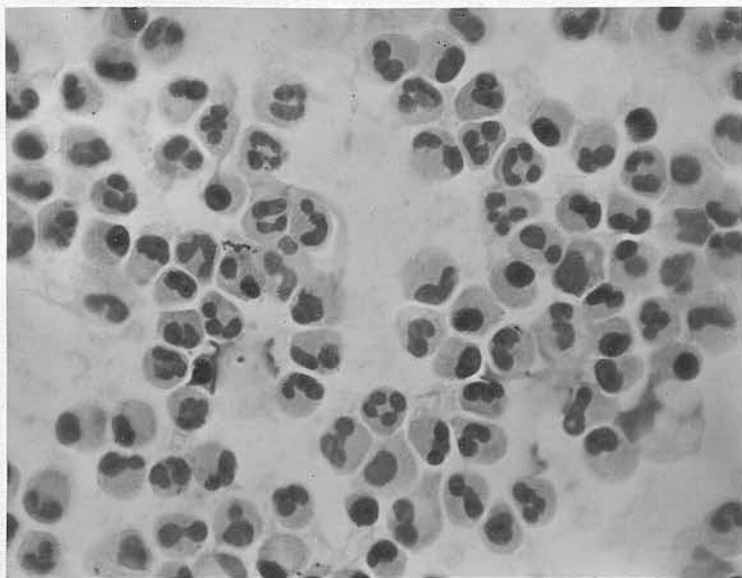


Fig. 19. Smear. H. and E. X 600.

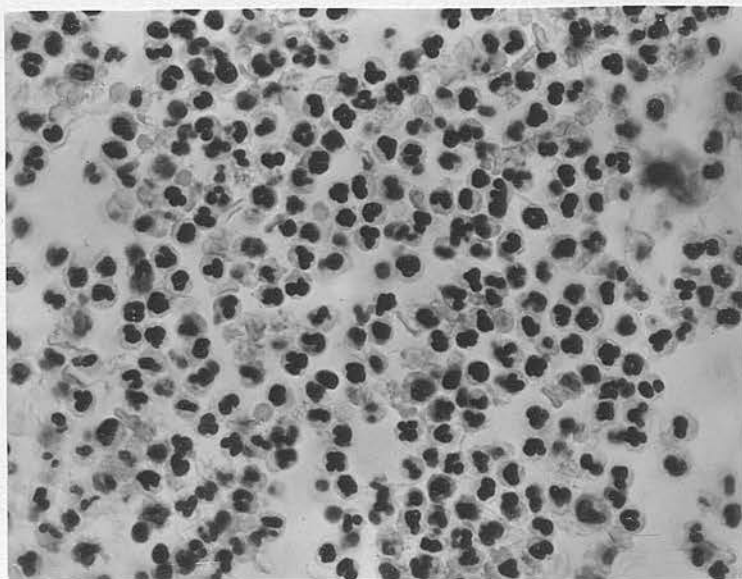


Fig. 20. Section. H. and E. X 600.

Smear and section from the same fluid at the same magnification. The fluid was simple inflammatory in origin. The marked shrinkage of polymorphs in the section is clearly demonstrated.

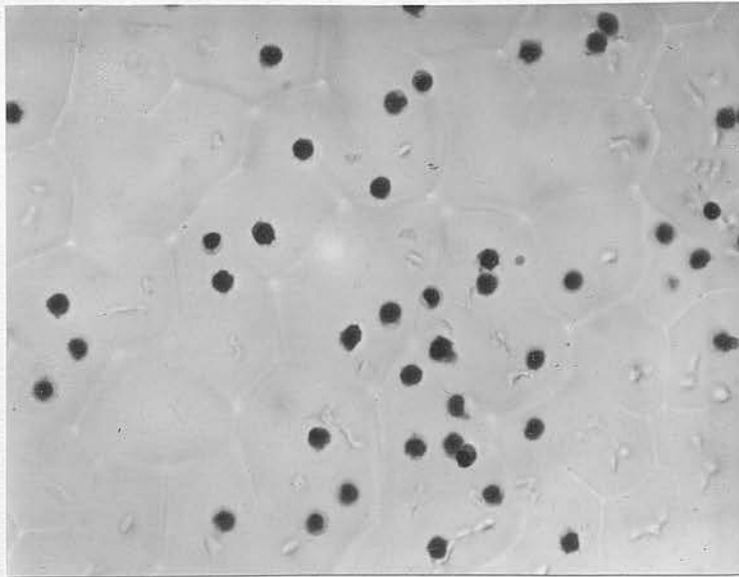


Fig. 21. Smear. H. and E. X 600.

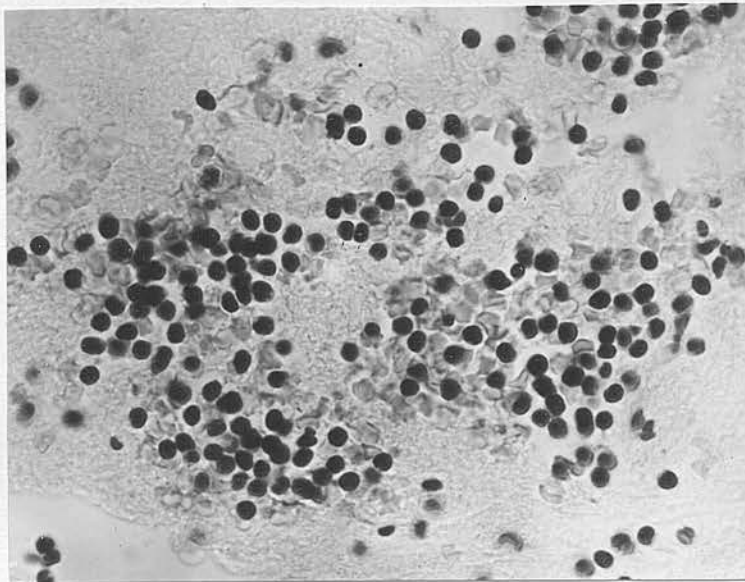


Fig. 22. Section. H. and E. X 600.

Smear and section from the same fluid at the same magnification. The fluid was tuberculous in origin. Lymphocytes do not shrink appreciably in the section.

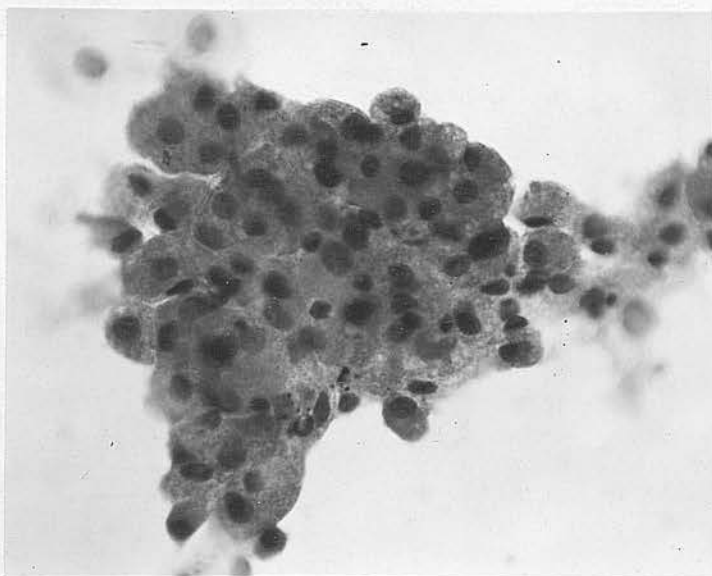


Fig. 23. Smear. H. and E. X 600.

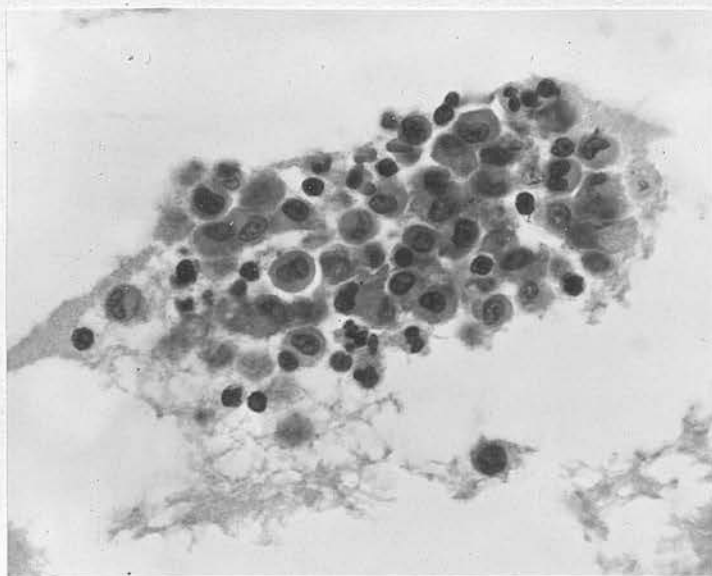


Fig. 24. Section. H. and E. X 600.

Smear and section from the same fluid at the same magnification. The fluid was a transudate containing mainly serosal cells. Shrinkage of cells is again demonstrated in the section, but this is more than compensated for by the greater clarity and definition of the over-all picture.

Subsequent illustrative photomicrographs are all of paraffin sections.

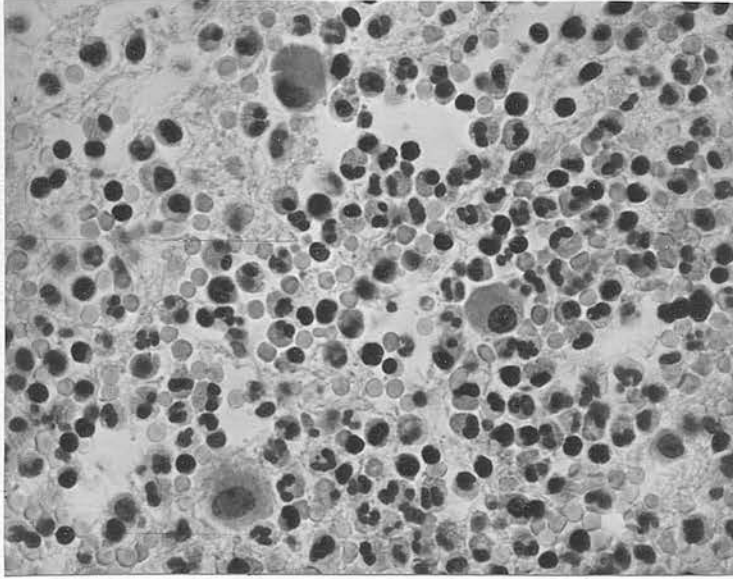


Fig. 25. H. and E. X 600.

This fluid proved to be tuberculous in origin. Polymorphs and lymphocytes are present in approximately equal numbers. Three large serosal cells stand out prominently in relation to the smaller cells; their uniformity of size, shape, nucleocytoplasmic ratio and depth of staining is characteristic.

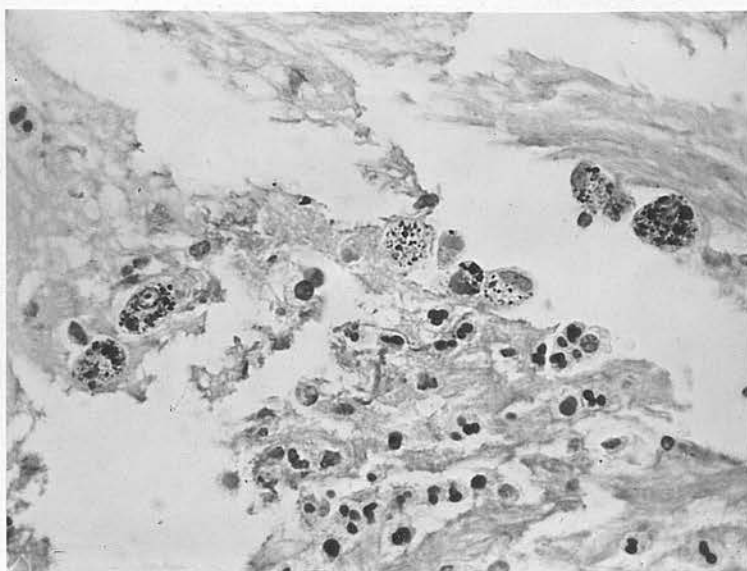


Fig. 26. H. and E. X 600.

This fluid was aspirated from a coal-miner with a post-pneumonic effusion. Several polymorphs are seen. The six larger cells are macrophages which have ingested carbon particles of varying size. The second macrophage from the left in the photograph shows a pale nucleus with a delicate nuclear membrane and a single small nucleolus. It is generally accepted that malignant cells do not exhibit such phagocytosis.

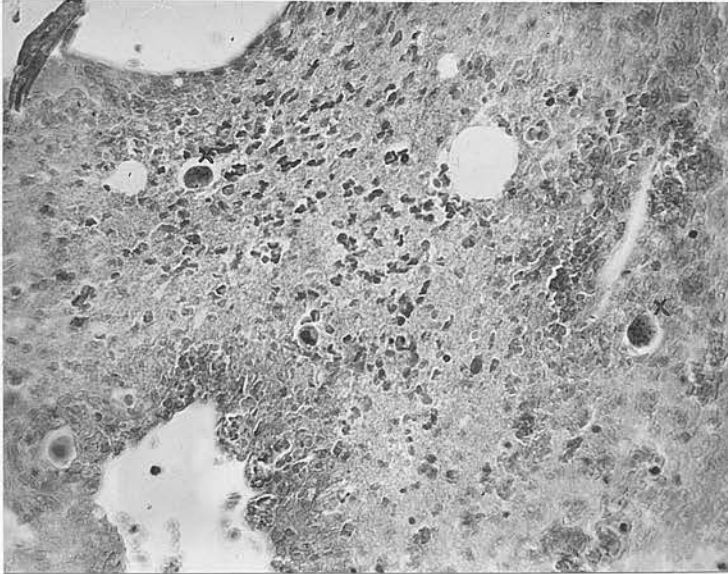


Fig. 27. H. and E. X 250.

In the midst of albuminous debris, red blood cells and a few lymphocytes, two larger cells containing small dark granules are seen. Under the microscope the granules were brownish in colour, making the cells identical in appearance with "heart-failure cells" often seen in sections of congested lung. The patient proved to have a transudate due to cardiac failure. The cells may have migrated from the lung.

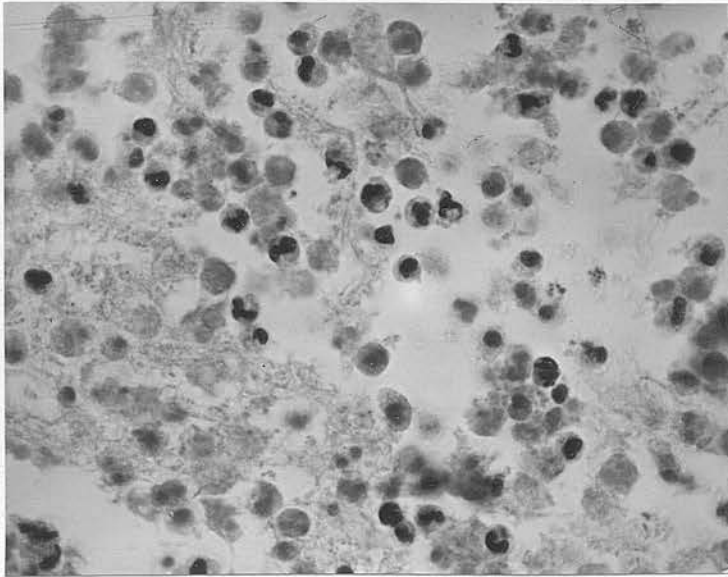


Fig. 28. H. and E. X 600.

This fluid was a frank empyema. Some polymorphs and an occasional lymphocyte can still be identified, but most of the cells have suffered autolysis so that only ghostly outlines and granular debris remain. It is futile to search for malignant cells in a section of this type even if the empyema is thought to be a complication of neoplasm.

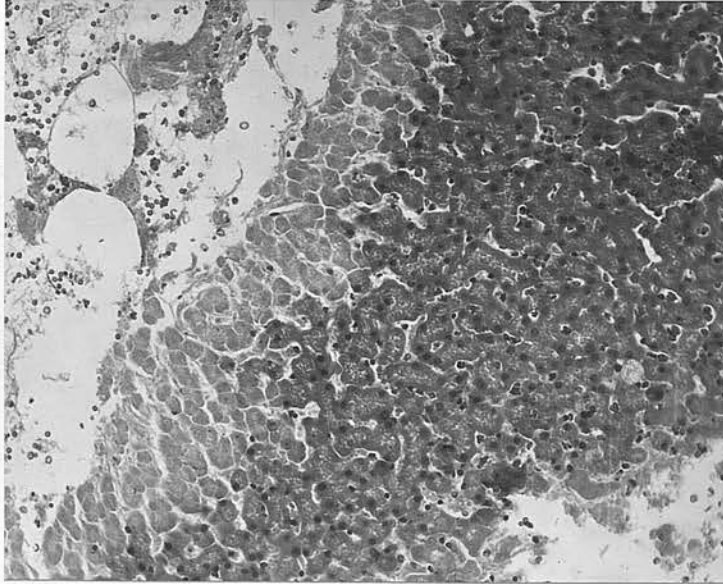


Fig. 29. H. and E. X 150.

Columns of liver cells, illustrating the ease with which liver biopsy can be performed by the transpleural route. The House Physician thought he had tapped a blood-stained pleural effusion.

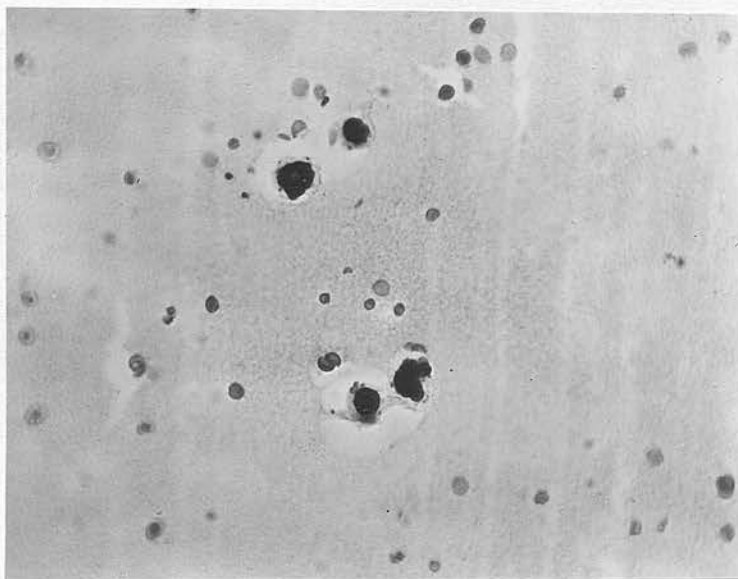


Fig. 30. H. and E. X 450.

Isolated dark "blobs" are occasionally seen in both malignant and non-malignant fluids. They are probably deposits of stain or possibly nuclear fragments extruded from cells. They should not be confused with actual cells with hyperchromatic nuclei.

It has already been pointed out that fluid due to pulmonary infarction was frequently stated by the pathologist to contain malignant cells. The next two photomicrographs, both of low magnification, show how the seeds of this error may be sown at initial scanning of the section.

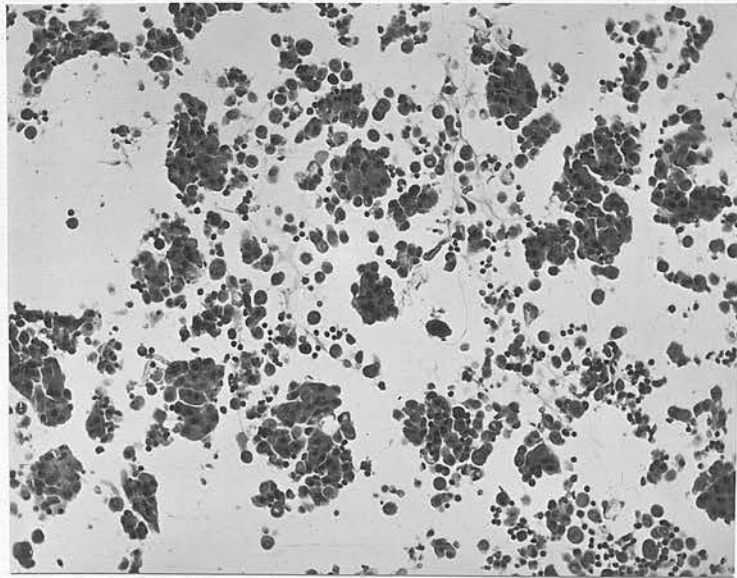


Fig. 31. H. and E. X 150.

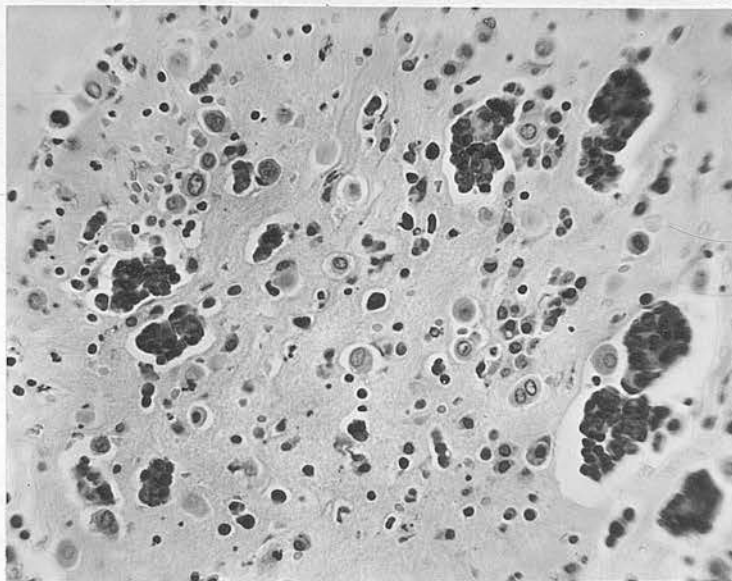


Fig. 32. H. and E. X 250.

Figure 31 is an infarction fluid. Sheets of serosal cells have been shed from the pleura, producing a distinctly unusual appearance closely

resembling clusters of malignant cells. Figure 32, for comparison, shows clusters of actual malignant cells in a carcinomatous effusion. It may be said, however, that even at those low magnifications, the hyperchromatic nuclei of the malignant cells are sufficiently distinctive to aid in the differentiation.

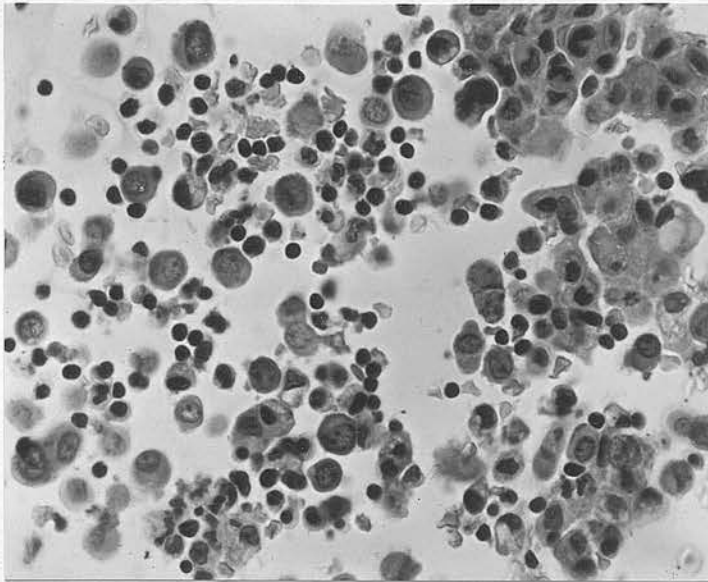


Fig. 33. H. and E. X 475.

This is a higher magnification of the serosal cells seen in Figure 31; numerous lymphocytes are also seen. This illustration should be compared with later illustrations of malignant cells at similar magnifications. In the meantime it is sufficient to emphasise the absence of pleomorphism of the cells and the absence of hyperchromatic nuclei.

Figures 34, 35 and 36 are further illustrations of serosal cells, the appearances of which must be absolutely familiar to the observer before identification of malignant cells is attempted.

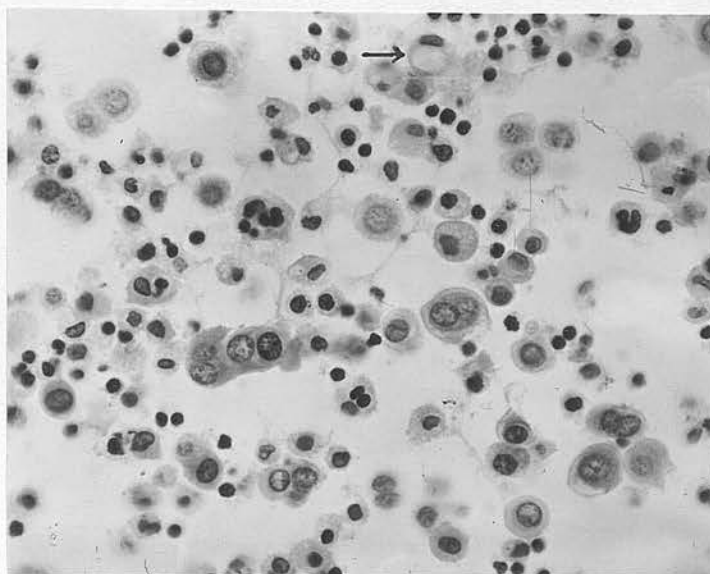


Fig. 34. H. and E. X 450.

Transudate

This is a particularly clear illustration of typical serosal cells admixed with lymphocytes. The following characteristics are noted:-

- i. Uniformity of size and shape of cells and nuclei; the nuclei are round.
- ii. Pale nuclei with delicate nuclear membrane.
- iii. Relatively small nuclei in relation to amount of cytoplasm.
- iv. Clear differentiation between nuclei and cytoplasm.
- v. Absence of syncytial mass of cells.
- vi. A "signet-ring" cell (arrowed) due to hydropic degeneration.

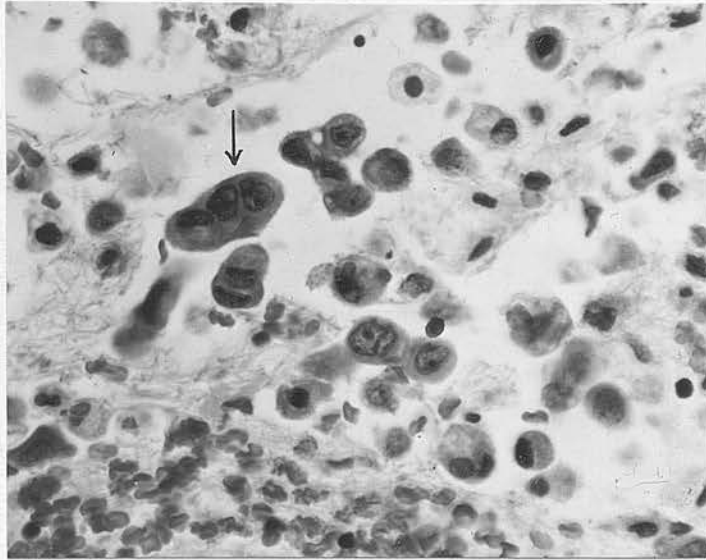


Fig. 35. H. and E. X 600.

Pulmonary Infarction

A serosal giant cell with three nuclei is arrowed. This appearance is not uncommon and is probably due to adherence of originally separate serosal cells.

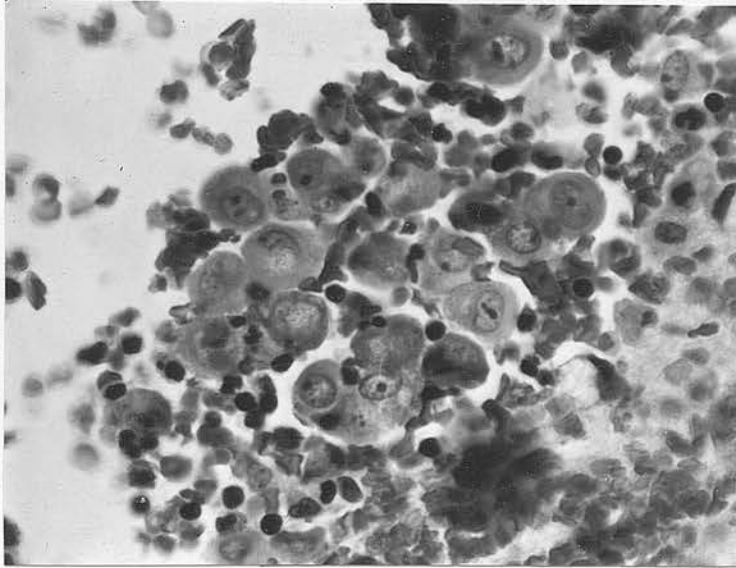


Fig. 36. H. and E. X 600.

Transudate

A group of unusually large serosal cells is seen. Although the thickness of the section has caused some super-imposition of cells, the characteristics described under Figure 34 are again demonstrated. In addition, many of the nuclei contain small but obvious nucleoli. It is important to note that the presence of nucleoli is not confined to malignant cells; in innocent cells, however, the size of the nucleoli is always small in relation to the size of the nuclei.

Figures 37 to 46 are illustrations of malignant cells.

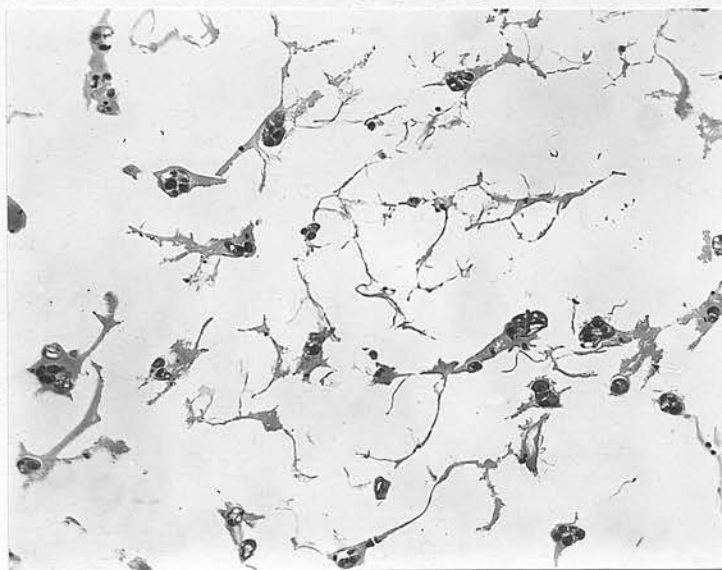


Fig. 37. H. and E. X 85.

Bronchial Carcinoma

The low-power scanning lens very often reveals groups of cells which stand out in the midst of other cells because of their hyperchromatic nuclei and/or syncytial arrangement. Such groups are highly suspicious of malignancy and demand closer study. In this particular section, suspicious groups are unusually conspicuous and numerous; indeed, scarcely any non-suspicious cells are present. It may be added that if no suspicious groups are seen on preliminary scanning, further search with a high-power lens is most unlikely to reveal malignant cells.

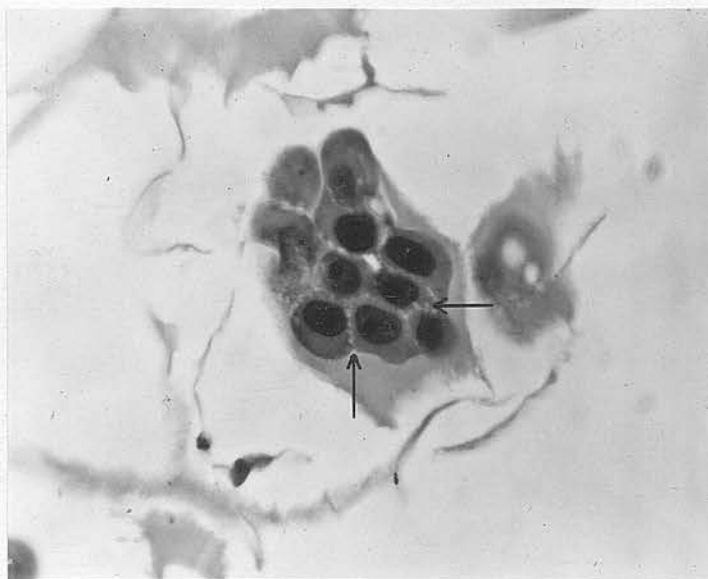


Fig. 38. H. and E. X 600.

Bronchial Carcinoma
(Same case as Fig. 37)

Higher magnification of one of the suspicious groups. The important features are

- i. Syncytial arrangement of cells.
- ii. Hyperchromatic nuclei.
- iii. Nuclei large in relation to amount of cytoplasm.
- iv. Relatively large nucleoli (also see Fig. 39).
- v. "Prickles" or cytoplasmic bridges between individual cells (best examples arrowed) indicating a squamous type of carcinoma. A squamous carcinoma was confirmed by bronchoscopic biopsy.

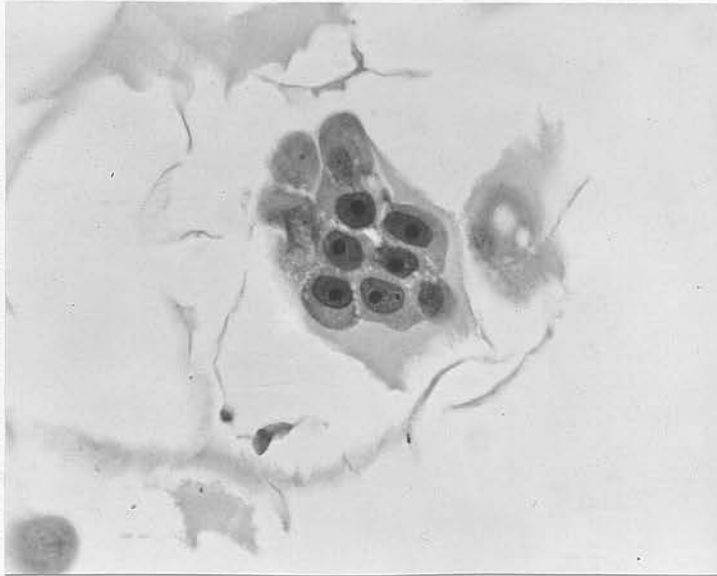


Fig. 39. H. and E. X 600.

Same case as Fig. 38

This print is a lighter reproduction from the same negative as Figure 38 designed to show the nucleoli more clearly. Their large size in relation to that of the nuclei is demonstrated. They should be compared with the innocent nucleoli in Figure 36.

Figures 40, 41, 42 and 43 are shown as a group followed by appropriate comments.

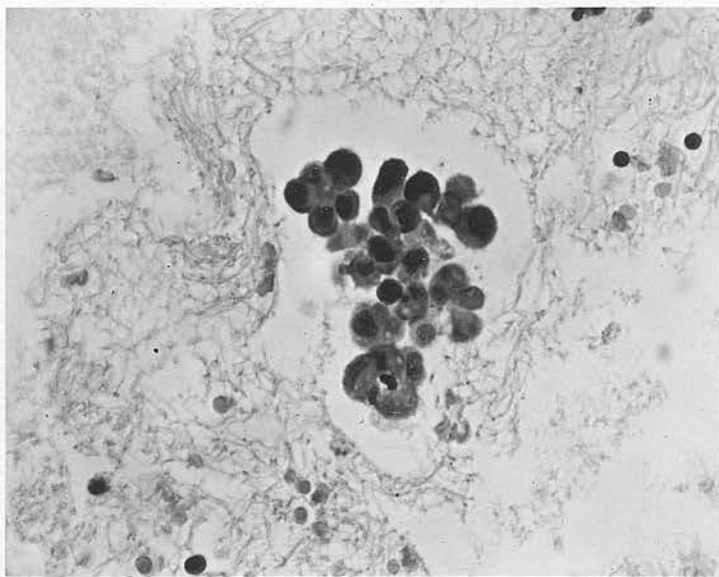


Fig. 40. H. and E. X 475.

Bronchial Carcinoma

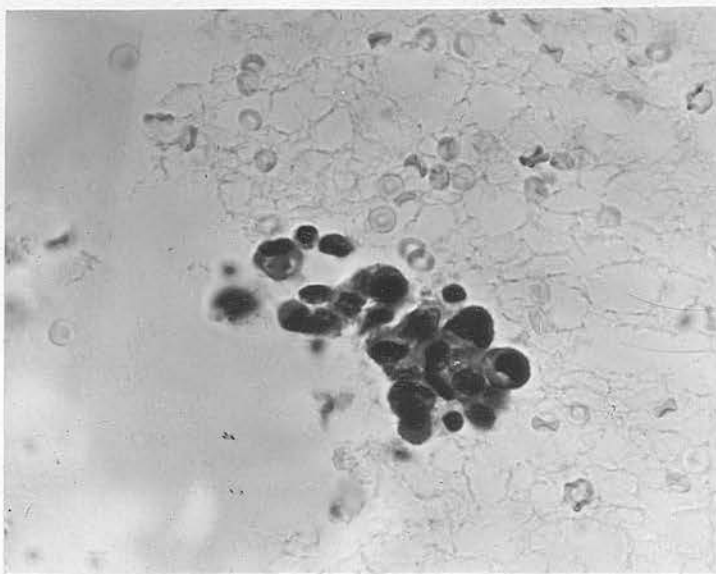


Fig. 41. H. and E. X 600.

Bronchial Carcinoma

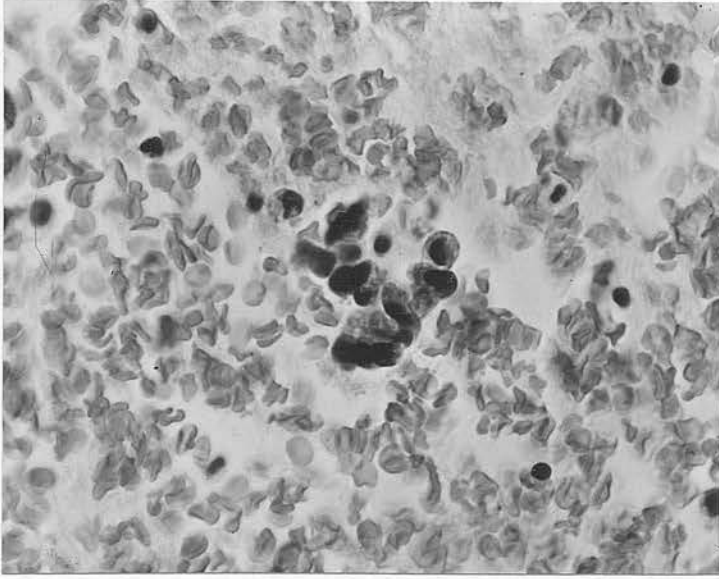


Fig. 42. H. and E. X 600.

Bronchial Carcinoma

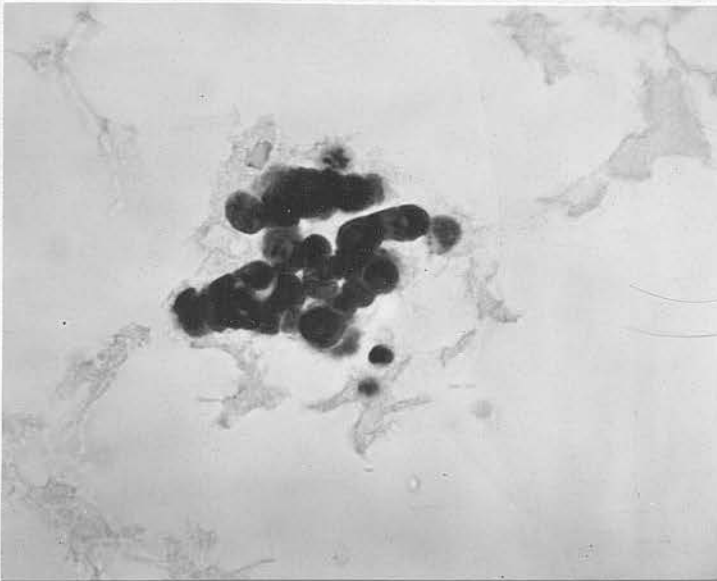


Fig. 43. H. and E. X 600.

Bronchial Carcinoma

Malignant characteristics are demonstrated as a uniform pattern in Figures 40 to 43, all from different fluids due to bronchial carcinoma.

1. In all, suspicious groups of cells were quickly picked out by the low-power scanning lens.

2. The cells show pleomorphism with regard to size, shape and nuclear configuration; many of the nuclei are kidney-shaped.

3. The nuclei are hyperchromatic and lack a clearly defined nuclear membrane.

4. The nuclei are large in relation to the amount of cytoplasm.

5. The nuclei are not clearly demarcated from the cytoplasm, giving a characteristic "smudged" appearance.

6. Nucleoli are conspicuous by their absence; they are not always observed in malignant cells.



Fig. 44. H. and E. X 450.

Bronchial Carcinoma

Bamforth (1946) has referred to a special feature of oat-cell bronchial carcinoma as found in sputum and pleural fluid, namely a granular appearance of the nuclei resembling stippling of red blood cells. Some of the cells in the fragment of carcinoma here illustrated probably show this feature. In addition, rather small nucleoli and a signet-ring cell are observed.

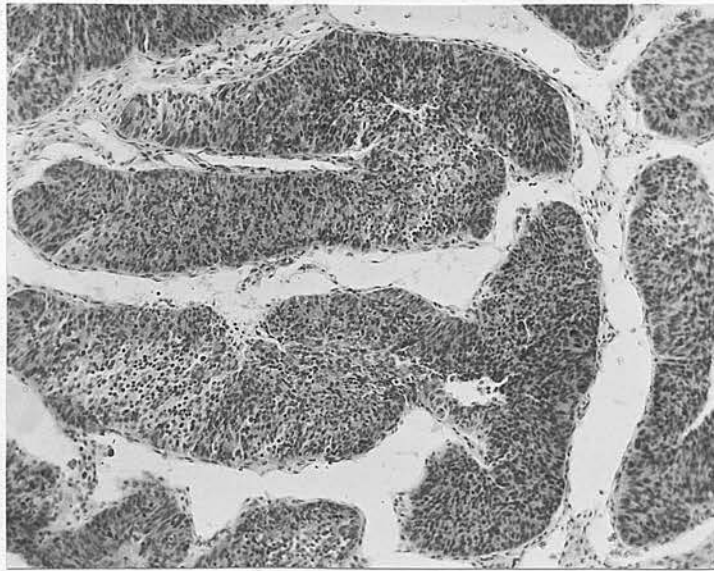


Fig. 45. H. and E. X 100.

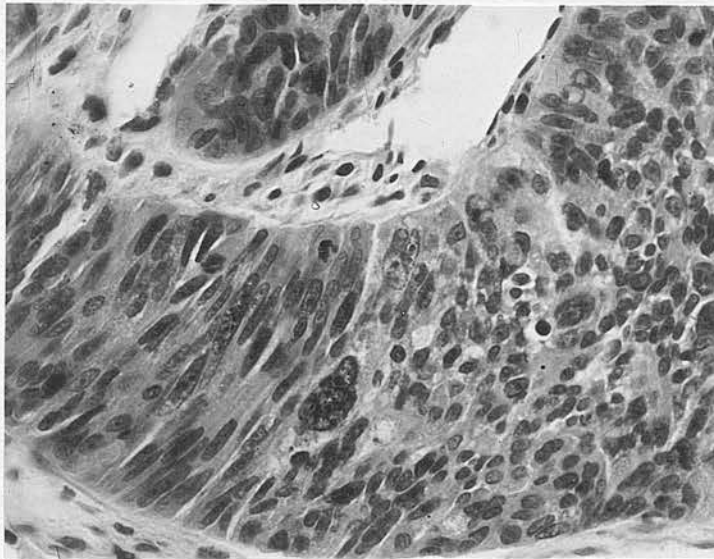


Fig. 46. H. and E. X 420.

Figures 45 and 46 are from the same case of bronchial carcinoma. The low magnification shows large tumour masses perhaps broken from the surface of the lung by the aspirating needle; while extremely helpful in diagnosis, this appearance must be excessively rare. The high magnification shows a syncytial mass of cells of which many have spindle-shaped nuclei; a tumour giant cell is seen in the middle of the picture. This slide was submitted to

Professor A.M. Drennan for a special opinion, since the author was unable to decide whether or not the cells could be distorted serosal cells. Professor Drennan stated that in his opinion the cells are undoubtedly carcinomatous, being unusual in appearance, but related to the squamous type.



Fig. 47. H. and E. X 600.

Transudate

This further illustration of serosal cells is included to re-emphasise their resemblance to malignant cells. Only careful consideration leads to the conclusion that the degree of pleomorphism and hyperchromatism of the nuclei is insufficient to establish a diagnosis of malignancy.

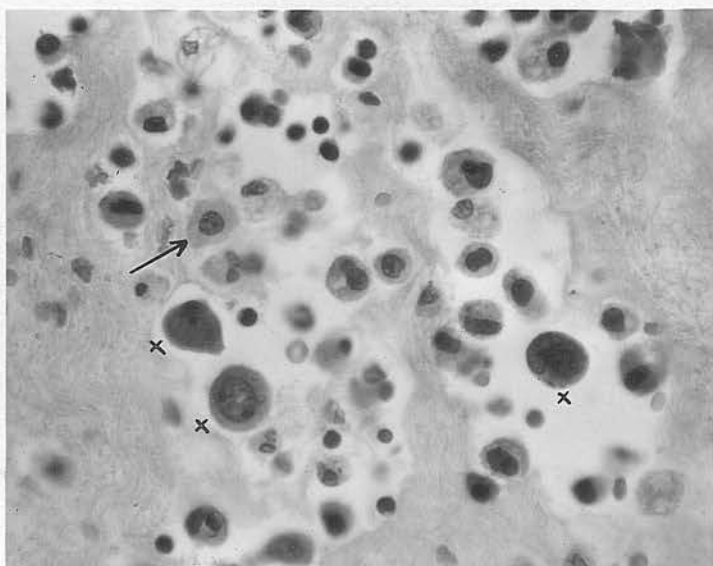


Fig. 48. H. and E. X 600.

Bronchial Carcinoma

Individual cells which may or may not be malignant present an insuperable problem in diagnosis. In this illustration, 3 large cells which differ considerably in morphology from an undoubted serosal cell (arrowed) are seen. Even so it is unwise to hazard a diagnosis of malignancy, since too many of the diagnostic features are absent; further, a serosal cell may occasionally assume a bizarre appearance. For safety, a border-line case such as this must be reported as "containing no undoubted malignant cells".

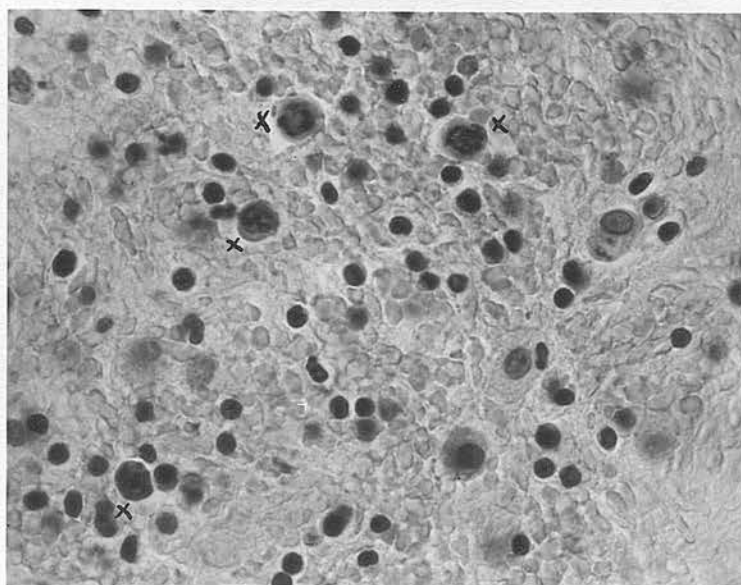


Fig. 49. H. and E. X 600.

Carcinoma of Pancreas with Malignant Pleurisy

The same problem as in Figure 48. 4 suspicious individual cells are indicated. At autopsy, secondaries were studded all over the pleura. Perhaps with increasing experience a less conservative attitude might be possible in this type of case.

Addendum. After this section was written, the opportunity occurred to study the pleural fluid from a patient with Hodgkin's Disease proved by lymph gland biopsy. Since pleural fluid in this disease is commonly a transudate due to lymphatic obstruction, no striking cytological picture was anticipated. This case, however, proved exceptional.

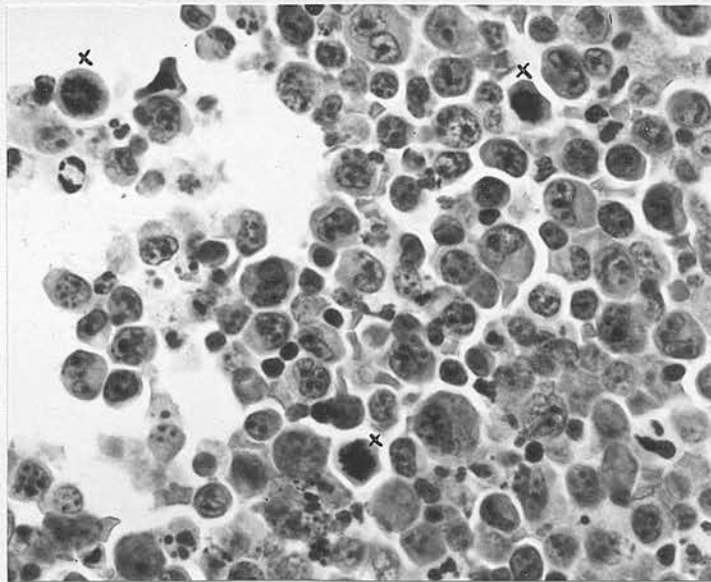


Fig. 50. H. and E. X 600.

Hodgkin's Disease

Apart from occasional lymphocytes, the cells are large and pleomorphic with pale nuclei; the nuclei contain scattered chromatin dots and in most cases a prominent nucleolus; multinucleated cells and 3 mitotic figures (indicated) are seen. The picture is that of a malignant form of Hodgkin's Disease. See also Figures 51 and 52.

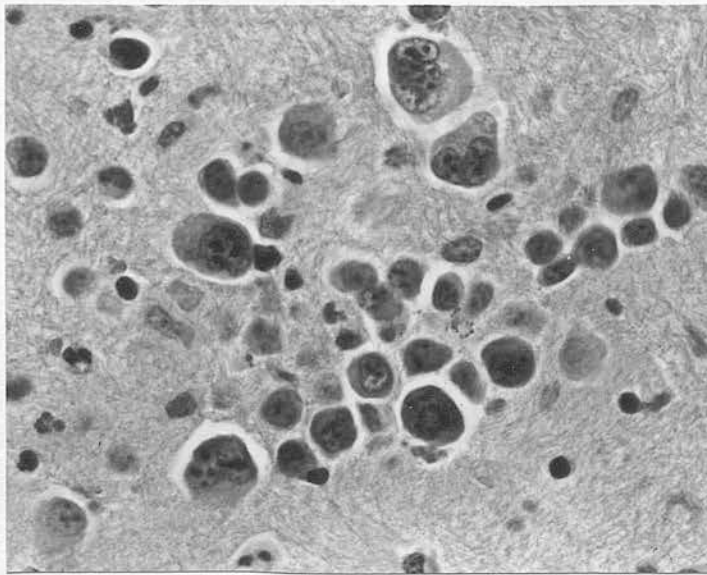


Fig. 51. H. and E. X 600.

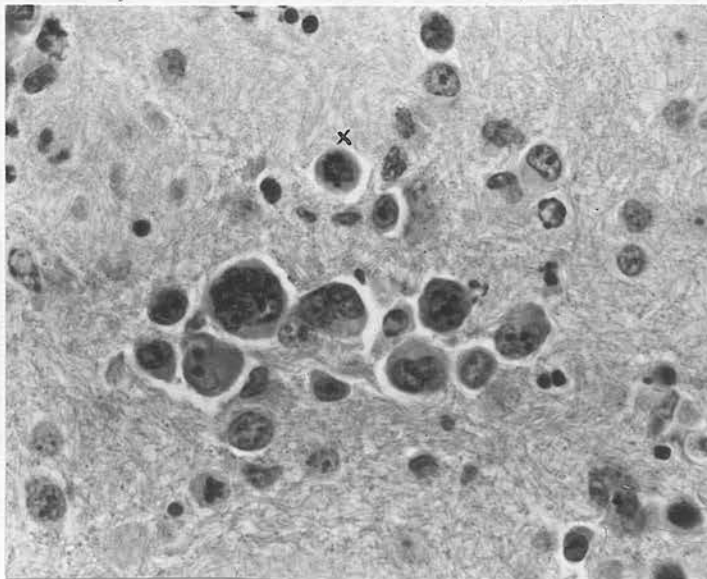


Fig. 52. H. and E. X 600.

Same case of Hodgkin's Disease as Figure 50.
Figure 51 shows typical multinucleated Hodgkin giant cells. Figure 52 shows giant cells and a mitotic figure (indicated).

Summary of Criteria for Cytological Diagnosis of Malignancy.

The re-examination of the hamatoxylin and eosin sections illustrated by the foregoing photomicrographs has shown that for the cytological diagnosis of malignancy the following criteria are of value.

1. Presence of an actual fragment of tumour.
2. Presence of groups of cells with hyperchromatic nuclei standing out among other cells under the low-power scanning lens.
3. Pleomorphism of such groups of cells with respect to size, shape and nuclear configuration.
4. Peculiarities of nuclei -
 - (a) Hyperchromatism
 - (b) Kidney shape
 - (c) Large size relative to amount of cytoplasm
 - (d) Lack of clear definition from cytoplasm
 - (e) Absence of distinct nuclear membrane
 - (f) ? Stippled appearance suggesting oat-cell type of bronchial carcinoma.
5. Nucleoli large in relation to size of nuclei.
6. Presence of cell bridges ("prickles") in squamous type of carcinoma.
7. Presence of numerous mitotic figures. This feature was surprisingly absent in the carcinomatous fluids, but was prominent in the one fluid due to reticulosis. Care is required in interpreting an occasional mitotic figure, since Foot (1937) reported

that this may be observed in an innocent serosal cell.

8. Presence of giant cells. Care is again required, since serosal cells may adhere to form giant serosal cells. Typical giant Hodgkin cells, however, are easily recognised.

In contrast to those criteria, signet-ring cells due to hydropic degeneration are common to both malignant and non-malignant fluids. Autolytic changes in frankly purulent fluids render the identification of malignant cells impossible. Single cells with apparently malignant characteristics cannot, in the present state of knowledge, be relied upon to establish a diagnosis of malignancy.

Retrospective Correction of Report by Pathologist.

Reference to Tables 9 and 10 recalls that of the 90 cases (111 fluids), the Pathologist reported malignant cells present in 37, of which 13 proved to be "false positives". Needless to say, in the re-examination of the sections, the "false positives" received special attention. In all, it was decided that in relation to the criteria enumerated above, the positive diagnosis had been made on insufficient evidence; in most instances it had been made on the presence of suspicious single cells, although in some, clusters of serosal cells due to pulmonary infarction

and cardiac failure had caused confusion. Of the remaining 23 "true positives", it was decided that in relation to the said criteria, 14 could no longer be held to have malignant cells present, the appearances being similar to those observed in non-malignant fluids. Of the 18 malignant fluids originally reported negative, it was decided that 1 could now be held to contain malignant cells. In the 1 fluid reported positive in which the ultimate diagnosis could not be established, it was decided that no malignant cells were present. Table 11 is a reconstruction of Table 10 with those corrections incorporated.

TABLE 11

Diagnosis	No. of Cases	Corrected Report	
		Malignant Cells Present	Malignant Cells Absent
Bronchial Carcinoma	27	7	20
Other Carcinoma	14	3	11
	41	10	
Transudate	17	0	17
Simple Inflamm.	16	0	16
Tuberculosis	7	0	7
Pulm. Infarct.	5	0	5
Meig's Syndrome	1	0	1
Undiagnosed	3	0	3
	90	10	80

The purpose of Table 11 is to show that of 41 proved malignant fluids, only 10 (24%) could be held to contain malignant cells. This statement requires certain qualifications -

1. The fluids were studied in retrospect with a knowledge of the ultimate diagnosis in each patient.
2. The only preparation of fluid examined was a paraffin section stained with haematoxylin and eosin.
3. An extremely conservative attitude to the cytological diagnosis of malignancy was adopted.
4. Although in all 41 patients a diagnosis of malignancy was ultimately established, it was not possible to prove conclusively that the pleural fluid was in all cases due to malignant invasion of the pleura. For example, in one patient, pleural fluid containing no obvious malignant cells was associated with carcinoma of the ureter; at autopsy there was no macroscopic or microscopic evidence of pleural or pulmonary metastases. Perhaps, therefore, a few of the 31 "malignant" fluids diagnosed as negative could not be expected to contain malignant cells.

The Use of Other Technical and Staining Techniques.

Papanicolaou (1946) makes passing reference to the use of his smear staining technique introduced originally for the early diagnosis of carcinoma of the uterine cervix. He states that "only a few thoracic and peritoneal fluids have been examined and

were mostly negative". The author is informed, however, by a recent visitor to Papanicolaou's laboratory in the United States of America, that the work on pleural and other fluids has been extended and that a descriptive atlas is about to be published. Bamforth (1946) has applied to pleural fluids the wet film technique, using Mayer's haemalum and eosin stain, originally introduced by Dudgeon and Wrigley (1935) for the detection of malignant cells in sputum.

The main advantage claimed for those methods is the more certain identification of individual and isolated malignant cells. If this claim is correct, it is clear that the percentage of cytological positives can be considerably raised, since with the method used by the author, fluids containing suspicious individual cells cannot be accurately assessed and hence have to be reported as negative. On the other hand, the methods, especially that of Papanicolaou, are time-consuming to the technical staff of a Pathology laboratory, and the interpretation of the preparations requires a specially trained cytologist. The ordinary Pathologist is unfamiliar with the appearances of such preparations. Further discussion on this problem is not indicated since the author confined his investigation to a method applicable to a Pathology department, the staff of which does not include a cytologist.

Practical Applications.

The ultimate test of any investigation is its practical value to the clinician. What then is the practical value of cytological diagnosis in malignant pleural effusion? Several points must be stressed in attempting to answer this question.

1. A pleural effusion due to malignant disease does not necessarily contain any malignant cells - for example in bronchial carcinoma the fluid may be secondary to lymphatic obstruction in the mediastinum.
2. Even if the fluid does contain malignant cells, the Pathologist, especially when using ordinary haematoxylin and eosin sections, may not be able to identify them positively as such.
3. Because of the influence of those two facts, the clinician should not expect too much of the Pathologist. The author's investigation indicates that only 24% of all malignant effusions can be diagnosed with absolute certainty by cytological examination.
4. Although 24% may seem a disappointingly low figure, it is probably still sufficiently high to justify the method of investigation, especially as, in certain cases, it may solve, without recourse to more complicated and - to the patient - unpleasant methods, a serious diagnostic problem.

5. From another point of view, 24% is a disappointingly high figure, since the finding of malignant cells indicates dissemination of the tumour and therefore a bad prognosis. Cytological diagnosis is not early diagnosis.

6. The problem of the "false positive" can be eliminated only by a conservative attitude on the part of the Pathologist. The risk of this error is greatest when the fluid is due to pulmonary infarction or to transudation, in both of which serosal cells cast from the pleura may individually or in clusters resemble malignant cells. Only by calling the doubtful case "negative" will the Pathologist eventually gain the confidence of his clinical colleague.

7. The clinician should keep in mind that the preparation of blocks and sections from pleural fluid means a great deal of time-consuming work to the technical staff of a busy Pathology laboratory. It is therefore suggested that a certain amount of selection should be exercised in the type of fluid sent for examination. The selection is best made by study of a simple Leishman film. If the cell picture is solidly lymphocytic or polymorphous, or if autolysis of cells is taking place, as in empyema, there is no point in troubling the Pathologist. On the other hand, the presence of

"serosal cells", especially in clusters, clearly justifies further investigation. Figures 8, 9 and 12 of the Leishman film investigation are illustrations of fluids of this type.

SECTION IIIBACTERIOLOGICAL INVESTIGATION OF PATIENTS WITH
PRIMARY TUBERCULOUS PLEURAL EFFUSIONA. Isolation of Tubercle Bacilli from the
Pleural Fluid.

Although it is now universally accepted that the "idiopathic" pleural effusion, especially in a young adult, is always or nearly always tuberculous in origin, this concept has not been based upon the frequent finding of the tubercle bacillus in the fluid. On considering the known facts about the evolution of the primary tuberculous effusion, it is easy to understand the relative failure of the Bacteriologist to clinch the diagnosis. The fluid, according to present-day opinion, is due to acute exudation from a hypersensitive pleura with consequent "dilution" of the few bacilli present. Clinicians are well aware of this difficulty and therefore do not expect much help from the Bacteriologist, although, for the sake of completeness, if not for diagnosis, they continue to send a specimen of fluid for examination. In order to determine the value of such examination carried out by ordinary routine technique in a Bacteriology department serving a large general hospital (Royal Infirmary of Edinburgh), the following investigation, referred to as the control investigation, was carried out.

Between 1946 and 1950, 66 pleural fluids from 65 cases, one bilateral, of primary tuberculous pleural effusion under the personal observation of

the author in various medical wards of the Royal Infirmary were examined by routine technique in the Bacteriology department. The technique was described as follows by the senior laboratory technician.

1. Each fluid, consisting of a specimen of approximately 10 c.c. clotted in a sterile test tube, was divided into two equal parts - 5 c.c. each.
2. First part centrifuged; films made from deposit and stained, i. Leishman (for cells) ii. Ziehl-Neelsen iii. Gram; remainder of deposit set up on culture for ordinary organisms.
3. Second part treated with 6% H_2SO_4 and centrifuged; deposit neutralised with NaOH and sown on ONE Lowenstein-Jensen slope. In some cases, at the request of the clinician in charge, the second part was used for guinea pig inoculation instead of Lowenstein-Jensen culture; in some cases the request form did not indicate that tuberculosis was suspected and hence investigation was not carried beyond the first part; in a few cases both guinea pig inoculation and Lowenstein-Jensen culture were done (although it would have been desirable to have as many cases as possible duplicated by guinea pig inoculation and Lowenstein-Jensen culture, no attempt was made to alter the laboratory routine in this respect).

The results of the control investigation are given in Table 12.

TABLE 12Control Investigation (Bact. Dept., R.I.E.)66 Tuberculous Pleural Fluids

Method	No. Examined	No. Positive	Percentage Positive
Gram Film and Culture for Secondary Organisms	66	0	0.00
Direct Film (Ziehl- Neelsen) for Tubercle Bacilli	66	1(1)	1.51
Lowenstein-Jensen Culture for Tubercle Bacilli	50(2)	8	16.00
Guinea Pig Inoculation for Tubercle Bacilli	21(3)	2	9.50

Note (1) Tubercle bacilli numerous; L.J. culture and G.P. inoculation not done; subsequently became tuberculous empyema.

Notes (2) & (3) Only 6 cases had BOTH done.

Both NEG.	4
G.P. POS.; L.J. NEG.	1
G.P. NEG.; L.J. POS.	1

Comments on Control Investigation.

1. Contamination of fluid by secondary organisms did not occur; special treatment of the fluid to avoid secondary growths on Lowenstein-Jensen cultures is therefore unnecessary.

2. Direct examination for tubercle bacilli was rarely positive.

3. Lowenstein-Jensen culture and guinea pig inoculation both showed a low positive percentage.

4. The diagnostic value of the routine technique of a laboratory serving a large general hospital is small in relation to the time, materials and laboratory space employed.

While the control series was going on, facilities given to the author in the Laboratory at Southfield Sanatorium, Edinburgh, were utilised for further investigation, referred to as the personal investigation. Several problems were considered before work was begun.

1. Guinea pig or culture? It was hoped to make a comparison of the two methods, but, at the time, 1946, guinea pigs were scarce and expensive, and it was therefore decided to concentrate on culture, using guinea pigs if and when available.
2. Which culture medium? The Lowenstein-Jensen medium was selected since it is easy to prepare or to buy and has proved reliable during many years of routine use by Bacteriologists.
3. Clotted or Citrated Fluid? The usual specimen received in a laboratory is 10 c.c. of clotted fluid. Presumably any tubercle bacilli present become entangled in the clot (c.f. the C.S.F. clot in tuberculous meningitis). Hence the clot should be placed on the culture medium. A clot, however, is often difficult to manipulate, and, if thick, may not centrifuge to the bottom of a tube. If the fluid is citrated, clot formation is prevented and a compact

mass is obtained on centrifuging. It was decided to use both clotted and citrated fluid.

4. Quantities. Reference has already been made to the dilution of tubercle bacilli in a large effusion. To overcome this, larger quantities of fluid were used.

Description of Personal Investigation.

Between 1946 and 1948, 40 pleural fluids were obtained from 40 cases of primary tuberculous pleural effusion under the personal observation of the author in the Royal Infirmary of Edinburgh. The 40 cases were in the charge of physicians whose permission could be obtained for the aspiration of a larger quantity of fluid than is usual. This fact governed their selection, but otherwise they were comparable to the cases of the control investigation in which similar permission could not readily be obtained.

From each case, 110 c.c. of fluid was divided as follows.

5 tubes, each with 10 c.c. of clotted fluid.

6 tubes, each with 10 c.c. of fluid prevented from clotting by the addition of 0.5 c.c.

3.8% sodium citrate.

One citrated tube was centrifuged and the deposit used for films (Gram; Ziehl-Neelsen) and for culture for ordinary organisms.

The other 5 citrated tubes were centrifuged separately and each deposit sown on a Lowenstein-Jensen slope.

The 5 clotted tubes were not centrifuged since initial trials showed that clots tended not to centrifuge down, or that if they did, they became tough and "unworkable"; each clot was simply caught up on a wire loop and sown on a Lowenstein-Jensen slope; in contrast to the control investigation, no treatment with H_2SO_4 was employed.

By this method, 10 Lowenstein-Jensen slopes were set up from each specimen of fluid, and incubated for six weeks.

When a guinea pig was available, an extra 20 c.c. of fluid was aspirated and prepared for inoculation.

Tables 13, 14 and 15 show the results of the personal investigation.

TABLE 13

Personal Investigation
40 Tuberculous Pleural Fluids

Method	No. Examined	No. Positive	Percentage Positive
Gram Film and Culture for Secondary Organisms	40	0	0.00
Direct Film (Ziehl- Neelsen) for Tubercle Bacilli	40	1(1)	2.56
Lowenstein-Jensen Culture for Tubercle Bacilli	40	21	52.50
Guinea Pig Inoculation for Tubercle Bacilli	16	2	12.50

Note (1) Tubercle bacilli were scanty; both L.J. culture and G.P. inoculation were NEGATIVE.

TABLE 14

Comparison of "Clot" and "Citrate" Cultures
(40 Tuberculous Pleural Fluids)

Clot	Citrate	Number
POS.	NEG.	14
NEG.	POS.	4
POS.	POS.	3
NEG.	NEG.	19
		40

TABLE 15

Comparison of L.J. Culture and G.P. Inoculation
(16 Tuberculous Pleural Fluids)

L.J. Culture	G.P. Inoculation	Number
POS.	NEG.	9
NEG.	POS.	1
POS.	POS.	1
NEG.	NEG.	5
		16

Comments on the Personal Investigation.

1. As in the control investigation, contamination of fluid by secondary organisms did not occur.
2. As in the control investigation, direct examination for tubercle bacilli was rarely positive.
3. Lowenstein-Jensen culture, using 10 slopes instead of 1 slope, showed improvement over the

control investigation. (52.5% positive against 16.0% positive).

4. With Lowenstein-Jensen culture, the "clot" method was, on the whole, better than the "citrate" method, although sometimes the "citrate" method was positive when the "clot" method was negative.

5. Of the 21 fluids positive on Lowenstein-Jensen culture, 11 showed a growth of tubercle bacilli on ONE slope only; the remaining 10 showed a growth on 2 or more slopes. This indicates the need for sowing a relatively large number of slopes.

6. Unfortunately, few guinea pig inoculations could be done. As in the control series, results were disappointing.

Comparison with Other Series Recorded in the Literature.

1. Close (1946) investigated 125 pleural fluids by Lowenstein-Jensen culture and by guinea pig inoculation. For culture, his technique varied over a period of years, in the last of which he used at least 8 Lowenstein-Jensen slopes, 7 being sown with clots and 1 with centrifuged deposit from citrated fluid; some of the clots were untreated and some were treated with H_2SO_4 or HCl . His final technique differed from the author's personal investigation in the following respects.

<u>Close</u>		<u>Author</u>
1. 8 L.J. slopes.	} At least.	10 L.J. slopes.
2. 7 clots; 1 citrate.		5 clots; 5 citrate.

<u>Close</u>	<u>Author</u>
3. Some clots treated with acid.	No treatment with acid.
4. Complete guinea pig comparison.	Incomplete guinea pig comparison.

Tables 16 and 17 give Close's results in comparison with the author's control and personal investigation.

TABLE 16

Tubercle Bacilli in Tuberculous Pleural Fluids

	Positive L. J. Culture (Per Cent)	Positive G. P. Inoculation (Per Cent)
Close	40.0	8.0
Author (Control)	16.0	9.5 ⁽¹⁾
Author (Personal)	52.5	12.5 ⁽²⁾

Notes (1) & (2) Percentages calculated from very small numbers.

The guinea pig results show agreement. The culture techniques of Close and the author show superiority over the control technique. The slight superiority of the author's personal culture technique over Close's technique is due to (1) the probable inclusion of a few non-tuberculous fluids in Close's series - he did not have his cases under personal observation (2) the fact that not all his fluids were subjected to his later and best technique; indeed, in the last year of his investigation, of 23 fluids, 16 (70%) were positive.

TABLE 17Comparison of L.J. Culture and G.P. Inoculation
(Close and the Author)

L.J. Culture	G.P. Inoculation	Number	
		Close	Author
POS.	NEG.	40	9
NEG.	POS.	0	1
POS.	POS.	10	1
NEG.	NEG.	75	5
		125	16

The superiority of Lowenstein-Jensen culture is conclusively demonstrated by Close's figures. The author's figures are very small in comparison, but at least show agreement.

2. Eberle (1949) cultured tubercle bacilli from all of 14 tuberculous fluids. His technique is extremely complicated. Essentially it consists of obtaining ten ounces of citrated fluid, and by means of repeated centrifuging, obtaining 12 deposits which are sown on 12 Lowenstein-Jensen slopes. Dr. Bowie (Bacteriology Department, Royal Infirmary) was kind enough in 1950 to give the author facilities to try out this method on a small series of 6 fluids. All 6 failed to grow tubercle bacilli. Apart from this lack of success, the main objection to Eberle's method is the inordinate amount of time required to investigate each fluid. It could not be done as a routine in a busy Bacteriology laboratory.

3. Karron and Purves (1947) cultured tubercle bacilli from 10 (20%) of 50 tuberculous fluids, but give no details of the technique used. On the other hand, they found guinea pig inoculation positive in 17 (53.1%) of 32 cases, a result in marked contrast to Close (8.0%) and the author (12.5%). Farber (1943) found guinea pig inoculation positive in 19 (28.8%) of 66 cases. Gloyne (1939), without giving figures, stated that he preferred guinea pig inoculation to egg medium culture.

B. Isolation of Tubercle Bacilli from Sputum or Gastric Juice.

In association with a primary tuberculous pleural effusion there may be a primary tuberculous complex in the lung and hilar glands, although such a complex has usually healed or is at least inconspicuous at the time of the effusion. Since the pulmonary and glandular components of the complex, even if present, rarely communicate with a bronchus, it is clear that the sputum or gastric juice of patients with primary tuberculous effusion will infrequently contain tubercle bacilli. The acceptance of this fact by clinicians is indicated by a study of the control series of 65 patients of whom none had more than a casual direct examination for tubercle bacilli of one or perhaps two specimens of sputum.

In the author's personal series of 40 patients,

only 2 could produce a suitable specimen of sputum for examination. In the remaining 38, a single specimen of fasting gastric juice was obtained. Each specimen of sputum or gastric juice was examined directly for tubercle bacilli, and, after concentration treatment with H_2SO_4 , set up on a single Lowenstein-Jensen slope. It is appreciated that the scope of this part of the investigation was limited - one specimen from each patient set up on only one slope - but the available materials were being used mainly for the fluid investigation. Guinea pig inoculation was not carried out. Table 18 shows the results.

TABLE 18

Sputum and Gastric Juice
40 Cases of Primary Tuberculous Pleural Effusion

Technique	No. of Cases	No. Positive	Per Cent Positive
Sputum - Direct	2	0	0.0
Sputum - L. J. Culture	2	0	0.0
Gastric Juice - Direct	38	0	0.0
Gastric Juice - L. J. Culture	38	2	5.3
All Methods	40	2	5.0

The two positive cases were also positive in the pleural fluid examination. Thus, in this series, the positives were not necessarily helpful in proving the tuberculous aetiology, merely duplicating the pleural fluid findings.

There is little information in the literature about such investigation of sputum or gastric juice. Eberle (1949) in a series of 140 cases also found Lowenstein-Jensen culture of gastric juice positive in 5%.

Discussion Relative to Sections A. and B.

This bacteriological investigation was undertaken with the knowledge that, from the nature of the pathology, cases of primary tuberculous pleural effusion do not readily yield up tubercle bacilli either from the fluid or from the sputum (gastric juice). It was hoped, however, to assess the value of routine techniques, and, if possible, to evolve a more successful technique. During the investigation, emphasis was placed on relatively simple methods, in the knowledge that cases of primary tuberculous pleural effusion are admitted in the first instance to general hospitals and that therefore the necessary bacteriology is undertaken, in the midst of other routine work, in busy laboratories in which complicated and time-consuming methods cannot be employed. Financial considerations have also to be kept in mind.

It was found that culture of the pleural fluid on Lowenstein-Jensen medium - author's technique - was the most successful method of isolating tubercle bacilli. 52.5% of fluids were positive in contrast to 16.0% of fluids positive in the control technique. The author's technique is simple and only moderately

time-consuming. 10 L.J. slopes are required, costing approximately one shilling each. Since special treatment of the fluid, e.g., by H_2SO_4 , is eliminated, the clinician, equipped with centrifuge and incubator, could easily carry out the procedure, even without the aid of a bacteriologist, in his own side-room. Sowing of clots is probably more successful than sowing deposits from citrated fluid, but the results show that it is probably advisable to use both methods. There is little doubt that the main reason for the superiority of the author's technique over the control technique is the use of more L.J. slopes.

Guinea pig inoculation of fluid, which was done in a limited number of cases in each of the author's and control series, proved disappointing, an average of 10.8% being positive in contrast to 52.5% positive and 16.0% positive with the author's and control culture techniques respectively. In addition to giving poor results, guinea pig inoculation is relatively time-consuming and expensive. Guinea pigs at present cost seven shillings each, and two are required for each fluid to have one in reserve in the event of a death from intercurrent infection, which is common. This means fourteen shillings per fluid in comparison with ten shillings per fluid for the author's culture technique. Even with those disadvantages, however,

it should be noted that in each of the control and author's series one fluid proved positive on guinea pig inoculation and negative on L.J. culture. This phenomenon is easily explained when it is remembered that growth of the bacillus in a guinea pig depends on virulence, while growth on culture depends upon other ill-understood factors. It is probable that pleural fluid contains antibodies - Wood (1937) - which in most cases render the bacillus less virulent and therefore less likely to infect a guinea pig. It is of interest that Karron and Purves (1947), who had marked success with guinea pig inoculation, encountered a considerable proportion of their cases in negroes, in whom tuberculous infections tend to be more virulent. The fact remains that, even in Great Britain, if guinea pig inoculation is not done, an occasional positive will be missed by L.J. culture.

Direct examination of fluid for tubercle bacilli is tedious and unrewarding work. It is almost not worth doing. The word "almost" must be used, because in the author's series one fluid on direct examination showed scanty tubercle bacilli which failed to infect a guinea pig and did not grow on culture. Presumably the bacilli were avirulent and also lacked the factors necessary for growth on the culture medium. In the control series, one fluid, which subsequently

became a tuberculous empyema, showed numerous tubercle bacilli on direct examination. Perhaps the finding of numerous bacilli should suggest the imminence of this serious complication.

In the author's series, investigation of sputum and gastric juice, albeit on a limited scale, was disappointing. Firstly, sputum is usually absent in such cases and the obtaining of gastric juice is liable to be opposed by the patient or made inconvenient by circumstances (e.g., over-worked nursing staff; investigation as an out-patient). Secondly, examination of sputum and gastric juice is technically time-consuming mainly because L.J. culture requires prior treatment of the specimen to secure concentration and to eliminate secondary organisms. Thirdly, direct examination was negative in all of the 40 cases and L.J. culture positive in only 2 (5.0%), both of which were duplicated by positive findings in the pleural fluid. It is certain, however, that in a larger series of cases, sputum or gastric juice would occasionally be positive in the presence of a negative fluid; indeed this has been observed by the author in 4 recent cases not included in the investigation. The above findings, together with those of Eberle (1949), who also found 5% of gastric juices positive on L.J. culture, suggest that L.J. culture of sputum or gastric juice is of diagnostic value in very few cases - varying

from 0% to 5% according to duplication of positives in the pleural fluid. Guinea pig inoculation, which was not used in this investigation, might well be more helpful.

Practical Applications.

This investigation has shown that for the efficient isolation of tubercle bacilli in cases of primary tuberculous pleural effusion the following routine is required:-

1. Direct examination of pleural fluid.
2. Culture of pleural fluid on 10 Lowenstein-Jensen slopes.
3. Guinea pig inoculation of pleural fluid.
4. Examination of sputum or gastric juice directly, by Lowenstein-Jensen culture and possibly by guinea pig inoculation (in this respect the investigation was limited to the barest minimum described above).

The second method will by itself give nearly all the positives (52.5%); the other methods will together add only an occasional positive. The cost of the second method in time and materials is not great; the third and fourth methods are costly in relation to the results obtained.

With regard to diagnosis, most clinicians would agree that the typical case of primary tuberculous pleural effusion in the young adult hardly requires bacteriological proof. It is suggested, therefore,

that time and materials should be saved by refraining from needless investigation in this type of case. They can thus be reserved for application of a thorough technique, as outlined above, to the aetiologically difficult case which commonly, but not always, occurs in older age groups. It is probable that thorough bacteriological investigation of the occasional "problem" case would cost no more than the commonly practised routine and less thorough investigation of all cases, and would give more help to the clinician.

SECTION IVPRIMARY TUBERCULOUS PLEURAL EFFUSION
IN OLDER AGE GROUPS

The primary serous pleural effusion in children and young adults no longer presents an aetiological problem. Many series of cases, carefully investigated and laboriously followed up, have been reported in the literature, leaving no doubt that, with few exceptions, the tubercle bacillus, although seldom declaring its presence in the fluid, is lurking in the background, prepared in later years to exact a further toll on the health of the victim.

A similar effusion in adults over 40 years of age presents a much greater problem in diagnosis, because of the lessening incidence of tuberculosis and the increasing incidence of malignant disease. From the statistical point of view it is clear that, unless care is taken at the outset to exclude malignant cases from consideration, morbidity and mortality occurring during a follow-up period, especially if the investigator is dependent on a postal questionnaire without necropsy control, may be wrongly attributed to tuberculosis. It is of interest in this connexion that Fauvet (1945), as a result of a follow-up of 731 cases of serous pleural effusion, believes that tuberculosis morbidity and mortality increase with

advancing years. On the other hand, Maclean (1948) fears that such a deduction may be erroneous, and that it is almost certainly due to the inclusion of a number of cases in which malignant disease is the real cause. The British Medical Journal (1946) points out that the prognosis with respect to the development of tuberculosis is much better in children than in young adults, but does not venture an opinion on adults over 40, in whom it states that "carcinoma of the lung is common".

Another statistical error may occur in all age groups, but more so in the older groups, if cases with the "adult" type of pulmonary tuberculosis complicated by effusion are included. As Thompson (1947) has pointed out, the prognosis in this type of case is that of pulmonary tuberculosis in general, and is therefore much worse than that of effusion occurring in the period after a primary infection. Radiology may fail to reveal an adult type of lesion until considerable absorption of the effusion has taken place; such a case may be wrongly included as a primary effusion.

The investigation described in this section was undertaken to determine the frequency and prognosis of primary tuberculous pleural effusion in patients over 40 years of age. Case material was selected from admissions to five medical charges in the Royal

Infirmary of Edinburgh during a period of five years from 1945 to 1949; in two of the five charges the period was extended to include 1950, 1951 and the early part of 1952. All patients aged over 40 found on admission to have a serous pleural effusion of uncertain aetiology were included initially in the investigation and total 75 in number. Cases in which the pleural effusion was secondary to some obvious lesion in the heart, lungs or elsewhere were excluded - except those in which the lung lesion was suggestive of the "adult" form of pulmonary tuberculosis. 2 of the 75 patients selected left hospital against advice before investigations could be completed, and were therefore omitted from the final analysis. The remaining 73 were carefully investigated and the follow-up is complete. Table 19 shows the ultimate diagnosis in these cases.

TABLE 19 /

TABLE 19Ultimate Diagnosis in 73 Cases of Pleural Effusion of Uncertain Aetiology occurring in Adults over 40

Diagnosis	No. of Cases
Bronchial Carcinoma	15
Tumours other than Bronchial Carcinoma	9
Simple Inflammatory	8
Collagen Disease	4
Cardiac Transudate	4
Reticulosis	2
Pulmonary Infarction	4
Adult Pulmonary Tuberculosis	2
Uncertain	1
Primary Tuberculosis	24
Total	73

Comments on DiagnosisBronchial Carcinoma.

Of the 15 cases, 2 were confirmed by necropsy, 3 by bronchoscopic biopsy, 1 by lymph gland biopsy, 1 by thoracoscopic biopsy and 2 by the later development of unequivocal radiological signs; the remaining 6 were less certainly confirmed by the development of probable radiological signs and/or a rapid downhill course with recurrence of blood-stained effusion and a fatal termination.

Tumours other than Bronchial Carcinoma.

Of the 9 cases, 4 were confirmed by necropsy, 1 by thoracoscopic biopsy, 1 by the development of undoubted (radiological) secondaries in the lungs, and 3 by the finding of malignant cells in the fluid associated with clinical or radiological evidence of a primary tumour elsewhere in the body.

Simple Inflammatory Cases.

All 8 cases had been treated with a sulphonamide and/or penicillin before admission and had clear sterile effusions without definite radiological evidence of lung consolidation. 5 were regarded initially as possible tuberculous effusions, 2 as possible simple inflammatory effusions (Cases 7 and 8) and 1 as a possible malignant effusion (Case 6). 5 cases had a predominance of polymorph neutrophils in the exudate, 1 a predominance of polymorph eosinophils, and 2 a predominance of lymphocytes. The subsequent course of events in each case was as follows.

Case 1. Initial pyrexia subsided with further sulphonamide and penicillin, but subsequently became hectic, with leucocytosis; eventual cure occurred with the coughing up of a large quantity of pus, suggestive of pulmonary or pleuro-pulmonary abscess.

Case 2. Pyrexia and fluid persisted. After discharge to a convalescent home the patient developed purulent sputum (negative for tubercle bacilli) and finger clubbing; subsequent investigation revealed a bronchiectatic lower lobe on the side of the effusion. The lobe was resected at thoracotomy, which revealed no evidence of tumour or tuberculosis;

the original effusion was lymphocytic.

Case 3. Pyrexia persisted and originally clear effusion became turbid; subsequent resection of empyema space showed no pathological evidence of tuberculosis.

Case 4. Pyrexia subsided rapidly with further sulphonamide. While convalescent the patient had a brisk haemoptysis. A radiological follow-up for four years showed gradual development of bilateral bronchiectatic changes.

Case 5. Pyrexia had subsided before admission. Effusion contained 70% eosinophils. The Mantoux test (1:100) was negative, and has remained so during repeated tests over two years.

Case 6. Pyrexia responded to further penicillin and sulphonamide; a subsequent relapse also responded. First aspiration - lymphocytes; second aspiration - lymphocytes plus possible malignant cells. The diagnosis of malignant disease was strengthened by the finding of a mass attached to the liver, but the patient was alive and well three years later. The mass is now thought to be an abnormal lobe of the liver. The condition is regarded as a simple inflammatory one because of the undoubted response on two occasions to sulphonamide and penicillin.

Case 7. In addition to pyrexia and left pleural effusion, the patient had hypertension and auricular fibrillation, but there was no evidence of either left- or right-sided cardiac failure. The effusion was clear and sterile, but with polymorph exudate. Pyrexia responded slowly to penicillin and sulphonamide; the effusion cleared up, but localized coarse crepitations appeared and persisted in the left lower lobe, indicating resolving consolidation (not visible on X-ray film). The patient died of congestive cardiac failure some months after discharge.

Case 8. 2 weeks after operative closure of a perforated duodenal ulcer, the patient developed a right pleural effusion with hectic pyrexia; the fluid was polymorphous but also contained an unusually large number of serosal cells. Serial X-rays showed the development of a fluid-gas level under the diaphragm (sub-phrenic abscess).

Collagen Disease.

Of the 4 cases, 1 presented with a bilateral

pleurisy which went on to bilateral effusion with high temperature; the provisional diagnosis was miliary tuberculosis, but necropsy showed unequivocal evidence of disseminated lupus erythematosus. 2 cases presented with joint pains and vague muscular pains, including chest pain, which was at first thought to be muscular in origin; both, however, developed bilateral effusion associated with a long continued toxic illness, and eventually showed changes in the hands diagnostic of rheumatoid arthritis. The remaining case presented with symptoms and signs of deficient peripheral circulation followed by bilateral pleurisy with effusion; the radiologist suggested that there were unusual chronic inflammatory changes in the lung fields; the skin eventually showed changes typical of scleroderma; it is probable that the effusions were due to chronic inflammation of the lungs secondary to scleroderma.

Although it is impossible to exclude tuberculosis in those cases, it is regarded as important that in each case the fluid was bilateral and was associated with subsequent undoubted evidence of a disease known to involve diffusely all the fibrous tissues in the body. Bilateral effusion in tuberculosis is uncommon. The problem of pleural effusion associated with collagen disease is discussed

in more detail later (see page 162).

Cardiac Transudate.

Since the diagnosis of a cardiac transudate is usually easy, it may seem odd that 4 cases with this condition presented considerable initial difficulty. Essential details of the cases illustrate how difficulty arose.

Case 1. This patient presented with slight dyspnoea and was found to have a left-sided pleural effusion. Neoplasm and tuberculosis were being considered when death occurred suddenly. At necropsy, an unsuspected cardiac infarct, approximately 3 weeks old, was seen to involve the left ventricle. There was no evidence of neoplasm, tuberculosis or lung infarct. The right pleural cavity was completely obliterated by old adhesions, thus accounting for the strictly unilateral nature of the transudate.

Case 2. This patient developed a left-sided pleural effusion following operative closure of a perforated duodenal ulcer; the radiologist reported that in addition to the effusion the lung fields showed inflammatory changes. The expected improvement with penicillin therapy did not take place; indeed both the fluid and the lung changes showed remarkable chronicity, and the patient was transferred to a medical ward for further investigation. An E.C.G. showed evidence of a myocardial infarction involving the left ventricle and corresponding in age to the date of the operation, although the patient had not complained of appropriate symptoms. Treatment with digitalis and a mercurial diuretic caused rapid clearing of the fluid and the "inflammatory" - i.e. oedematous - changes in the lungs.

Case 3. This patient was admitted for investigation of a left pleural effusion. Although the history was highly suggestive of left ventricular failure, neoplasm was favoured in diagnosis because of (a) haemorrhagic fluid on aspiration (b) high protein content of fluid (c) malignant cells reported in fluid by Pathologist (d) absence of radiological evidence of congestion in lung fields (e) absence of an obvious cause for left ventricular failure. Subsequent necropsy showed rheumatic aortic valvular disease with no evidence of neoplasm, tuberculosis or pulmonary infarction.

Case 4. This patient presented with a puzzling

interlobar effusion which eventually proved to be cardiac in origin. The case is reported in detail in a subsequent section (see page 145).

Reticulosis.

One case presented with a right pleural effusion which was thought to be tuberculous in origin. Some months later signs of superior mediastinal obstruction and generalized lymphadenopathy developed; a gland biopsy showed a lymphoid follicular reticulosis, in which serous effusion is a common finding (Hadfield and Garrod, 1947). The other case was known to have a reticulosis of obscure type, gland biopsy suggesting the possibility of atypical Hodgkin's disease. Bilateral pleural effusion developed in the absence of radiological evidence of thoracic gland involvement. In view of the possible confusion pathologically between Hodgkin's disease and tuberculosis, the latter was considered in diagnosis. The effusions, however, proved to have a low protein content; this led to estimation of the plasma proteins, when the albumin was found to be 2.29 g.%. A high protein diet corrected the low plasma albumin, and the pleural fluid disappeared. It seems reasonable to conclude that the pleural effusions were transudates due to hypoproteinaemia complicating a reticulosis.

Pulmonary Infarction.

As with cardiac transudate, unexpected difficulty may arise in the initial diagnosis of pleural effusion due to pulmonary infarction. Essential details of the 4 cases are given.

Case 1. This patient was in a hospital ward for investigation of gall-bladder disease. While in bed she developed an acute pleurisy, with subsequent rapid development of a clear serous effusion; there was no evidence of pneumonia. Haemoptysis appeared on the third day of illness. A pulmonary infarction seems the most probable diagnosis in view of the haemoptysis and the onset of illness while in bed; there was, however, no evidence of thrombophlebitis, and tuberculosis had been considered prior to the haemoptysis.

Case 2. This patient was admitted for investigation of a left pleural effusion. The history was of steadily increasing dyspnoea over a period of 3 weeks associated, in the last week, with an irritating

cough and slight haemoptysis. The diagnosis from the history was quite clearly bronchial carcinoma, and this seemed to be confirmed by the finding, on diagnostic aspiration, of a heavily blood-stained fluid which was said by the Pathologist to contain large numbers of malignant cells. Necropsy revealed, not a bronchial carcinoma, but a massive pulmonary infarction secondary to a myocardial infarction involving the right ventricle and corresponding in age to the beginning of her illness.

Case 3. This patient developed obvious thrombophlebitis of the veins of the left leg some weeks AFTER an acute right pleurisy with effusion. When the fluid absorbed, serial X-rays of chest showed a clearing opacity in the right lower lobe consistent with a pulmonary infarction. It is realised that the thrombophlebitis may have been the result of a primary chest illness, but the veins of the affected leg were varicose and it is therefore probable that a low grade thrombophlebitis existed prior to the development of obvious symptoms and signs. In any event neoplasm was excluded by follow-up, and tuberculosis seems unlikely in view of the radiological findings.

Case 4. This patient was admitted for investigation of a right pleurisy with effusion. Although the patient had not complained of it, there was an obvious thrombophlebitis of the veins of the left leg. Diagnostic aspiration revealed a haemorrhagic fluid which was said by the Pathologist to contain malignant cells. A provisional diagnosis of bronchial carcinoma with complicating thrombophlebitis was made. One week later there was a recurrence of right pleuritic pain followed by haemoptysis. All the clinical features resolved with anti-coagulant therapy, and follow-up has excluded the existence of neoplasm. It is virtually certain that pulmonary infarction is the correct diagnosis.

Adult Pulmonary Tuberculosis.

Two cases had radiological changes in the lungs suggestive of this condition; in both, the sputum was found to contain tubercle bacilli. It should be noted that the number in this group is artificially small, as such cases are not admitted to the Royal Infirmary of Edinburgh if alternative accommodation can be obtained.

Uncertain.

This patient, known to have hypertension, was resting in bed at home. She developed a febrile illness with pleuritic pain and copious purulent sputum, and a clear serous lymphocyte effusion subsequently occurred. All investigations for tuberculosis were negative. A follow-up for four years showed recurrent bronchitis, asthma, obesity, and hypertension. As the main illness took place at home and she was seen only when the effusion was clearing up, it is difficult to suggest a diagnosis: "simple inflammatory" seems a more probable diagnosis than tuberculosis.

Primary Tuberculosis.

Of the original 73 cases, 49 have been described above, leaving 24 in which a diagnosis of primary tuberculosis was made. It should not be thought, however, that this diagnosis rests entirely on a process of exclusion. Of those 24 cases, 16 had an illness resembling in every respect the classical primary tuberculous effusion in the young adult - that is, sudden onset, in an apparently previously healthy person, of acute pleuritic pain progressing to a serous effusion, with no radiological evidence of lung disease, and pursuing a protracted febrile course unresponsive to sulphonamides and/or penicillin. Five others of the 24 had a similar illness, but the onset was more insidious, and there was little or no pleuritic pain - in 1 of the 5 there was a preceding episode of erythema nodosum. Of the remaining 3 cases, one had an acute pleurisy progressing to effusion without pyrexia at any time; another had only dyspnoea, and aching pain on the side of the effusion; the third had no chest

symptoms whatever, the effusion being diagnosed during screening at a barium meal examination arranged because of vague dyspepsia.

In only 2 cases was the tubercle bacillus isolated from the pleural fluid; this does not invalidate the diagnosis, since only 1 fluid of the 24 was subjected to the thorough technique outlined in Section III, and it is known that in similar cases in young adults it is difficult to isolate the bacillus unless special methods are used. Only 1 case had tubercle bacilli isolated from the sputum or gastric juice. X-ray films of the chest after clearing of the effusion did not reveal any case of adult pulmonary tuberculosis. Follow-up has excluded any disease, other than tuberculosis, which might have accounted for a pleural effusion.

Frequency of Primary Tuberculous Pleural Effusion
in Older Age Groups.

In this series of 73 cases of serous pleural effusion of initially uncertain aetiology occurring in adults over 40 years of age, only 24 could be ascribed to primary tuberculous infection. 24 proved to be secondary to malignant disease of the lungs or elsewhere. Only 2 were due to the adult form of pulmonary tuberculosis, but this is an artificially small number because of the restricted admission of this type of case to a general hospital. Details of the remaining 25 cases have been included to justify

their grouping under miscellaneous conditions given in Table 19.

As stated earlier, this series of cases was selected from admissions to five medical charges during a period of five years from 1945 to 1949 - in two of the charges the period was extended to 1952. In order to find the relative frequency of primary tuberculous effusion in adults over 40, the corresponding numbers of cases of primary tuberculous effusion in young adults admitted to the same five charges over the same period of time were determined. The details are given in Table 20. It should be noted that children under the age of 12 are not admitted to the Royal Infirmary of Edinburgh.

TABLE 20

Age Distribution of 236 Cases of Primary
Tuberculous Pleural Effusion

Age (Years)	No. of Cases	Per Cent
Under 20	126	53.4
20 - 29	66	28.0
30 - 39	20	8.5
40 - 49	12)	5.1)
50 - 59	5) 24	2.1) 10.1
60 - 69	6)	2.5)
70 - 79	1)	0.4)
Total	236	100

It is observed that, excluding children, in whom tuberculous pleural effusion is in any case relatively uncommon, approximately 10% of primary tuberculous effusions occur in adults aged over 40. Of the 24 patients aged over 40, 15 were males and 9 females.

Pathogenesis of Primary Tuberculous Pleural Effusion in Older Age Groups

It is difficult to estimate how many people in Great Britain over 40 are tuberculin-negative. Recent tuberculin surveys have concerned children and young adults, but in 1934 Kayne found that among non-tuberculous admissions to a general hospital in London 15% of the 45-59 age group and 14% of the over-60 age group were tuberculin-negative. Those figures are probably artificially high, as it is well known that debility and intercurrent illness in hospital patients may inhibit the tuberculin reaction. In a recent paper from Norway, Jonsen and Ustvedt (1950), using a combination of Mantoux and B.C.G. tests, conclude that lack of tuberculous allergy in old people is not so common as has been assumed, being in the region of 12%. McPhedran and Opie (1935) found that in approximately 5% of adults who failed to react to tuberculin, X-ray of chest revealed calcified tuberculous foci; they conclude that in those circumstances the lesions may be regarded as obsolete.

While there may be some doubt about the precise

number of older people liable to acquire a primary infection, Terplan (1940), in his pathological studies, has proved beyond question that primary infection does occur. Of 23 adults with a primary complex demonstrated at necropsy, 11 were over the age of 40, one being aged 80. Terplan in addition has shown that an older person may acquire a "second" primary infection when the "first" primary infection has become completely calcified and inactive - presumably with reversion to tuberculin negativity; he describes the necropsy findings of 14 such cases over the age of 40; in all, the "second" infection was anatomically distinct and separate from the calcified remains of the "first" infection. Kayne, Pagel and O'Shaughnessy (1948) believe, further, that an old primary infection may commonly flare up in people over 45 years. It would seem, therefore, that a primary tuberculous effusion may occur in older people following

- i. Delayed primary infection.
- ii. Reactivation of old primary infection.
- iii. "Second" primary infection.

In the present series of 24 cases, 1 case which came to necropsy showed reactivation of a primary Ghon focus. Most of the 24 had lived in large cities since early childhood and therefore had every opportunity of acquiring infection earlier in life. No case had a history of recent contact with a known

source of infection. Only 1 case showed radiological evidence of hilar gland enlargement, this being the only point in which the clinical picture differed from that of similar effusions in young adults, in whom such radiological evidence is slightly more common - 8 of 76 cases under the age of 40 observed by the author. This difference has been noted previously - Landau (1949) - and may mean that in the older person a typical primary complex, in which hilar gland enlargement is usually marked, is not commonly present. Indeed Pagel (1948), from the pathological point of view, states tentatively that in adults there is a tendency for the glandular component of a primary complex to be smaller than the lung component - the reverse of the finding in children. It is not possible to draw conclusions from this present series of cases, but it would seem that delayed primary infection, in its typical form, is probably not an aetiological factor.

Prognosis in Primary Tuberculous Pleural
Effusion in Older Age Groups

While it has been proved - Graham (1925), Smithers (1934), Vaizey and Perry (1940), Landau (1949) - that primary tuberculous effusion in children has a surprisingly good prognosis, there is little agreement in the literature concerning the influence of advancing years. It is unfortunate that many series in the literature, especially those dealing with selected groups of young adults - e.g. in

the Services - include no cases older than 40, and that those which do, have, of necessity, all too few for statistical purposes. The old enemies, inadequate follow-up and doubtful diagnosis, also play a part in invalidating statistics. There is a tendency too for older patients to develop and to die from diseases unconnected with the original tuberculous illness.

Thompson (1946), whose series of 190 cases included only 13 over 40 years of age, considers that age per se does not matter with respect to the development of frank tuberculous lesions. Vaizey and Perry (1940) rightly do not venture an opinion, since, of 49 patients over 40 years of age, 23 could not be traced or had died of an unknown cause. In contrast to Thompson, Fauvet (1945) believes that, in France, tuberculosis morbidity increases with advancing years; he gives the following percentage for each age group without stating the actual number of cases from which the percentage figure is derived:

<u>Age Group</u>	<u>Percentage T.B. Morbidity</u>
0 - 19	8.4
20 - 29	10.0
30 - 39	11.6
40 - 49	16.5
50 - 59	22.5
60 - 69	not given

Gaarde (1930) and Farber (1943) believe that in those

over 40 years of age there is a tendency for the prognosis to become worse. Maclean (1948) comes to no conclusion on this point, but fears that the inclusion, in error, of a certain number of malignant cases, may artificially increase the mortality rate.

Unfortunately, the present series of 24 cases over 40 years of age is also small, but efforts have been made to eliminate errors in diagnosis and follow-up is complete. All surviving patients have been examined clinically and radiologically, and necropsy has been performed on most of those who died. Table 21 gives the results of follow-up.

TABLE 21

Follow-up of 24 Cases of Primary Tuberculous
Pleural Effusion in over-40 Age Group

	<u>No. of Cases</u>
Alive and well	11
Dead - Pulmonary Tuberculosis	2
" - Miliary "	2
" - Pericardial "	1
" - Addison's Disease	1
" - Coronary Thrombosis	1
" - Cause Unknown	1
Alive - Active Pulm. Tuberculosis	4
" - Inactive " "	1
	<hr/> 24 <hr/>

Of the 11 alive-and-well patients, 1 actually suffered a recurrence of pleurisy with effusion on

the contralateral side, but has otherwise shown no sign of frank tuberculosis.

Of the 8 dead patients, 6 (in bracket) were proved by necropsy to have died of tuberculosis, 1 through the effects of destruction of the suprarenal glands. The remaining 2 did not come to necropsy; in 1 the final illness was in all respects typical of coronary thrombosis; in the other, no details of the final illness could be obtained.

Of the 24 patients, therefore, 11 (46%) suffered tuberculous morbidity, and 6 (25%) eventually died of their tuberculosis. Although no sweeping deductions can be made from this small series, it is at least clear that primary tuberculous effusion is a potentially serious disease in older people. The morbidity figure of 46% compares unfavourably with that of 26% in a series of 76 patients under 40 years of age observed by the author in the same hospital over the same period of time.

The Nature of the Subsequent Tuberculous Lesions

Of the 11 patients with subsequent frank tuberculosis, 3 obviously suffered haematogenous dissemination from the initial infection - miliary tuberculosis (2), suprarenal tuberculosis (1). Although pericardial tuberculosis may be due to local invasion from the nearby lung or pleura, there was no evidence of this in the patient with pericardial

tuberculosis who came to necropsy; it is therefore tempting to assume, and such an assumption would be in keeping with modern pathological opinion, that the pericardial lesion was also haematogenous in origin.

Cameron (1952), in a Honyman Gillespie Lecture delivered in Edinburgh, pointed out that lung tuberculosis following a primary pleural effusion is of two types

- i. Typical so-called reinfection subclavicular type which leads to bronchogenic tuberculosis.
- ii. Bilateral apical type which is PROBABLY of blood-borne origin and which leads so often to sluggish lung tuberculosis long confined to the upper lobes.

It is of interest that of the 7 patients in this series who developed lung tuberculosis, 4 showed the bilateral apical type suggestive of blood-borne origin. 2 of the remaining 3 showed, at necropsy, bilateral extensive bronchogenic tuberculosis, while the other remains well with an inactive unilateral subclavicular infiltration.

It is clear that any deduction from this analysis must be regarded as tentative only. It seems, however, that there is a tendency for older patients with primary tuberculous effusion to develop subsequently frank tuberculosis of a type in some cases certainly, and in other cases possibly due to

haematogenous dissemination.

Practical Applications:

1. In a series of 73 patients over 40 years of age presenting with a serous pleural effusion, approximately one third (24) proved to have a primary tuberculous effusion; in the remainder the effusion proved to be secondary to some other condition. Approximately 10% of all primary tuberculous pleural effusions occur in adults over 40. Those facts should be kept in mind during the investigation of serous pleural effusion in an older patient, in whom there is perhaps too great a tendency to diagnose malignant disease.

2. Difficulties in assessing the prognosis of primary tuberculous effusion in older age groups have been stressed, but there is suggestive evidence that subsequent tuberculous morbidity is greater in them than in children and young adults. That the potential gravity of such an effusion in the older patient is perhaps not fully appreciated is illustrated by the fact that only 10 of the 24 patients received a period of treatment at a convalescent home before being returned to normal life; and in only 4 was that period longer than one month (it so happens that 3 of those 4 are alive and well). It may be that the bad prognosis in this series is partly due to this factor. In comparison, virtually all children and young adults with effusion treated at

the same hospital over the same period of time had a prolonged period of convalescence. It would seem that efforts should be made to secure adequate convalescence for all cases of effusion, irrespective of age.

Appendix.

Of the 24 patients, 1 was of exceptional interest and perhaps merits a brief case report.

P.T., a male aged 74, was first admitted to the Royal Infirmary of Edinburgh in January, 1945. He had taken ill acutely with right pleuritic pain and fever. He was found to have a right pleural effusion (Fig. 53); diagnostic aspiration revealed a clear serous fluid. The subsequent progress was that of a primary tuberculous effusion and he was eventually discharged in good health.

He was not seen again until September, 1948, when he was re-admitted with extreme dyspnoea, praecordial pain and auricular fibrillation; clinical and radiological examination (Fig. 54) showed gross cardiac enlargement. He was thought to have a coronary thrombosis with cardiac dilatation. Death occurred suddenly after 4 weeks during which there was a swinging temperature to 100° F..

At necropsy the principal findings were

- i. A large haemorrhagic pericardial effusion with chronic tuberculous thickening of the pericardium.
- ii. Fibrous obliteration of the right pleural sac in keeping with the former pleural effusion.
- iii. A reactivated primary tuberculous complex in the right upper lobe and related lymph nodes.



Fig. 53.

Chest X-ray of P.T., aged 74, in January, 1945, showing a massive right tuberculous pleural effusion. The absence of mediastinal shift at first raised a suspicion of associated pulmonary collapse due to neoplasm, but, after clearing of the fluid, the underlying lung was found to be normal. The calcification observed at the left border of the heart is almost certainly in an atheromatous coronary artery.



Fig. 54

Chest X-ray of P.T., now aged 77, three years later (September, 1948). There is residual fibrosis in the right pleural sac. The gross enlargement of the heart shadow was noted, but pericardial effusion was not considered in diagnosis since the clinical picture was more suggestive of coronary thrombosis with cardiac dilatation. There is no radiological evidence of the reactivated primary complex found on the right side at necropsy.

SECTION VCARDIAC PLEURAL TRANSUDATE AS A PROBLEM IN DIAGNOSIS

The typical case of cardiac transudate presents no problem in diagnosis. The pleural fluid, which may be unilateral or bilateral, is clear and serous, has a low protein content and usually has a predominance of serosal cells; an easily detected cardiac lesion is present, and the patient shows other evidences of cardiac failure. From time to time, however, the author has been asked to investigate patients with cardiac transudate in whom certain difficulties prevented an early appreciation of the correct diagnosis. From the point of view of effective therapy, it is essential that a cardiac transudate should not be erroneously regarded as a pleural effusion due to some other less treatable cause, and hence it is considered justifiable to review those patients in whom difficulty arose.

Case 1. A female patient aged 60 was admitted to hospital on 13. 6.47. For two months she had complained of anorexia, cough, mucoid sputum, night sweats and increasing dyspnoea on exertion; there was no history of pleuritic pain or swelling of the ankles. On examination she was obviously dyspnoeic; there was a large right pleural effusion with mediastinal shift to the left; apart from some distension of the neck veins and a faint mitral systolic murmur, there was no clinical evidence of cardiac disability; B.P. was 175/115; pulse was rapid but regular. Diagnostic aspiration revealed a clear serous fluid which was sterile on culture and contained 90% lymphocytes; protein content was 1.2 Gms. per 100 mls.. For the first five days in the ward she had

a slight irregular pyrexia to 99°F..

Because of the history of night sweats and the slight pyrexia, the Physician-in-charge favoured a diagnosis of tuberculosis.

A chest X-ray on 16. 6.47 (Fig. 55) showed a right pleural effusion with cardiac enlargement and possibly congestive changes in the lung fields. This picture, in association with the low protein content of the pleural fluid and the absence in the history of pleuritic pain, seemed to justify a provisional diagnosis of cardiac transudate; treatment with digitalis and mersalyl was instituted with marked beneficial effect. A chest X-ray on 26.6.47 (Fig. 56) - 10 days later - showed complete clearing of the fluid and congestive changes.

Comment. In retrospect, this patient presented no great difficulty in diagnosis. She was obviously suffering from hypertensive left ventricular failure, although certain features suggested a tuberculous illness. The value of careful assessment of the chest X-ray is emphasised.

Case 2. A female patient aged 47 was admitted to hospital on 12. 9.47. She was in good health until 3 weeks before admission when she had an attack of "bilious" vomiting which went on for 2 days; thereafter she developed an irritating cough with steadily increasing dyspnoea. On examination she was obviously dyspnoeic; there was a large left pleural effusion; the cardio-vascular system appeared normal; B.P. was 100/65. Diagnostic aspiration revealed a slightly hazy fluid which was sterile on culture and contained equal numbers of lymphocytes and serosal cells; protein content was 2.9 Gms. per 100 mils.. She was not fit enough to have a chest X-ray. Portable E.C.G. - standard leads only - showed a sinus bradycardia with an occasional ventricular extrasystole.

After one week in the ward, during which repeated therapeutic aspiration of the left pleural cavity was required, she died suddenly. The provisional diagnosis was bronchial carcinoma, but necropsy showed the following.

1. Myocardial infarction of approximately 3 weeks standing involving the wall of left ventricle and interventricular septum.

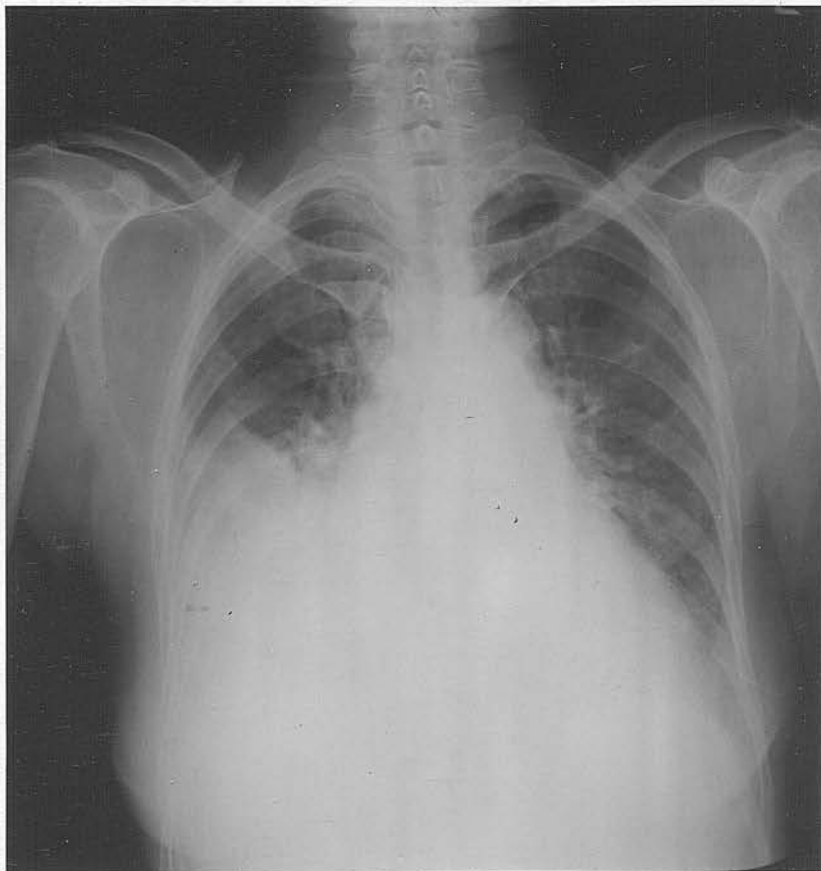


Fig. 55. Case 1.

Chest X-ray on 16. 6.47 showing right pleural effusion with cardiac enlargement and possibly congestive changes in the lung fields. Although the left costo-phrenic angle is a little obscured, there was no clinical evidence of fluid in the left pleural cavity.

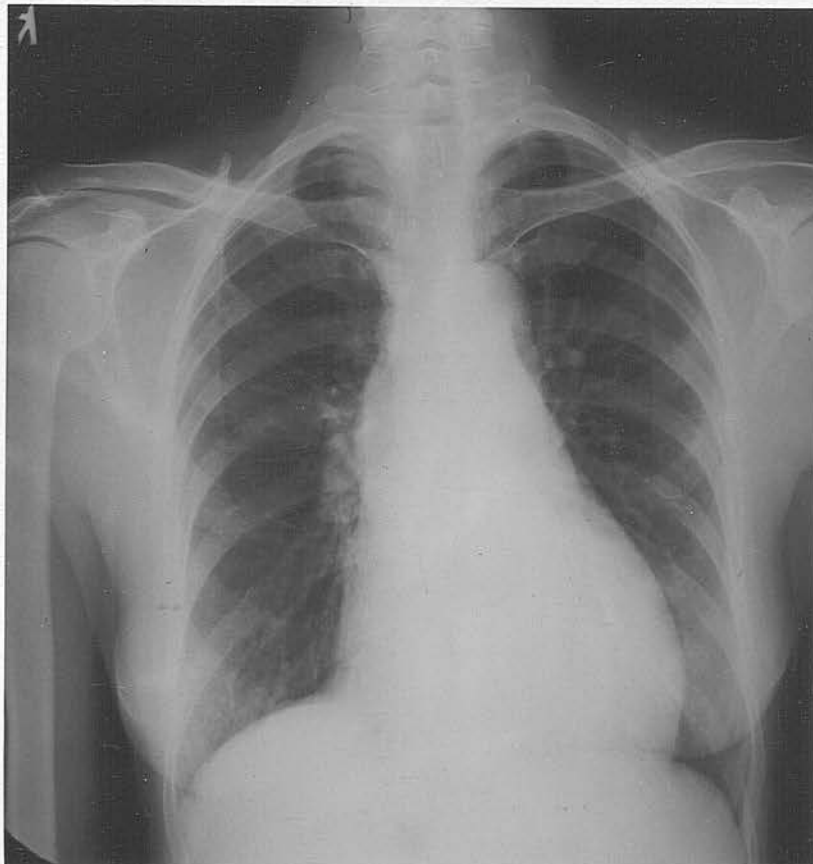


Fig. 56. Case 1.

Chest X-ray on 26. 6.47 - 10 days after Fig. 55. Treatment with digitalis and mersalyl has caused rapid clearing of the right pleural effusion and congestive changes in the lung fields. Slight cardiac enlargement persists.

- ii. Large collection of fluid in left pleural cavity.
- iii. Complete obliteration of right pleural cavity by old adhesions.

Comment. In retrospect, it is clear that the attack of "bilious" vomiting represented the onset of myocardial infarction. A more complete E.C.G. study would probably have established the diagnosis during life. The protein content of the fluid was not sufficiently low to arouse suspicion of a transudate. In this patient, the obliteration of the right pleural cavity necessitated the unilateral nature of the transudate.

Case 3. A male patient aged 68 was referred to hospital as an out-patient on 19.11.48. For some months he had felt vaguely unwell with loss of appetite, but without any complaint referable to the cardio-vascular or respiratory systems. His past health had always been good, except for an attack of jaundice two years previously, diagnosed as infective hepatitis. Clinical examination was normal. A Barium meal showed no abnormality, but during screening the radiologist observed an opacity in the chest. Because of this, a chest X-ray was taken and showed (Fig. 57) an effusion between the upper and middle lobes on the right side; the cardiac shadow was seen to be enlarged.

Despite the negative chest history, the possibility of an interlobar empyema was considered, but diagnostic aspiration revealed a clear fluid which was examined with the following results: sterile on culture; no clot on standing; protein 1.25 Gms. per 100 mls.; and cell content, 100 per cu.mm. with 70% serosal cells and 30% lymphocytes. The fluid was considered to be a transudate of unknown aetiology. No treatment was prescribed.

The patient reported on 10.12.48. He now complained of dyspnoea on exertion. Clinical examination showed bilateral basal crepitations which had not been present previously; the cardio-vascular system was again found to be normal (no clinical evidence of the cardiac enlargement known to be present could be found). An X-ray of chest (Fig. 58) showed a considerable increase in the interlobar

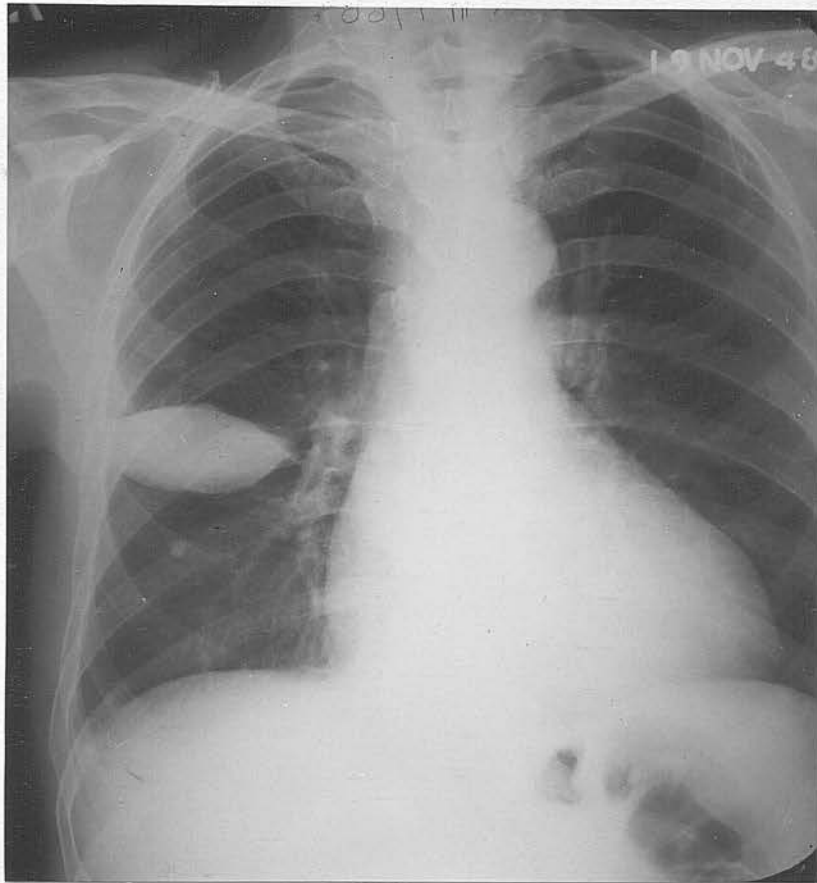


Fig. 57. Case 3.

Chest X-ray on 19.11.48 showing a pleural effusion loculated between the upper and middle lobes on the right side. There is cardiac enlargement, but no evidence of congestion in the lung fields. This X-ray was taken during screening at a Barium meal examination at a time when the patient had no symptoms referable to the cardio-vascular or respiratory systems.

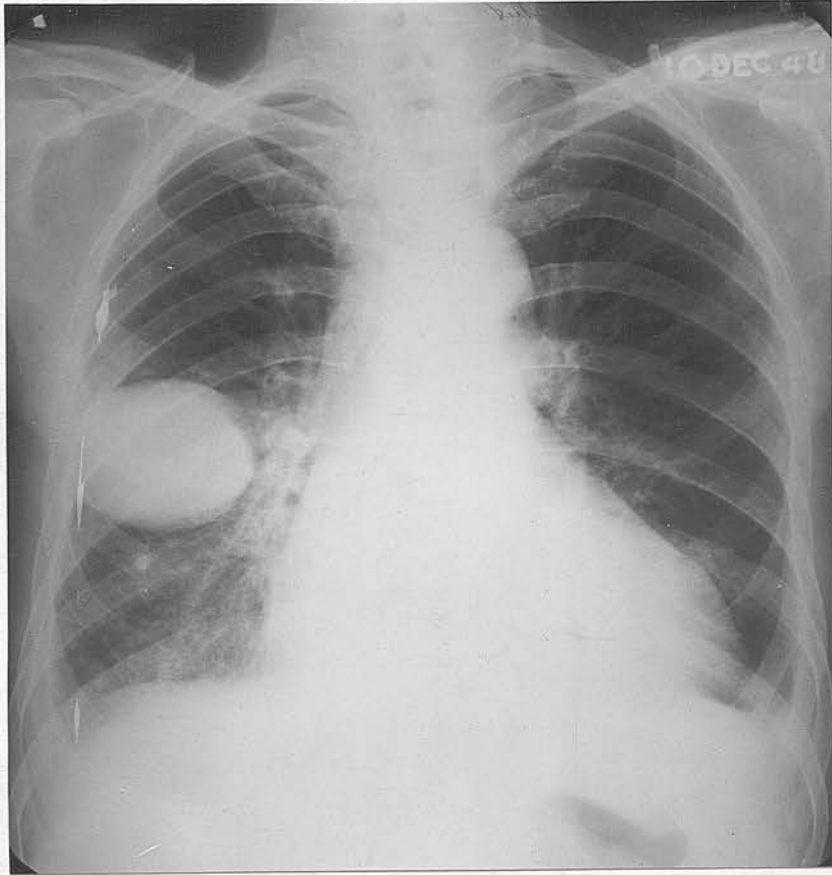


Fig. 58. Case 3.

Chest X-ray on 10.12.48 following the development of dyspnoea and basal crepitations. The interlobar effusion is larger. Both costo-phrenic angles are obscured. The lung fields show slight congestion.

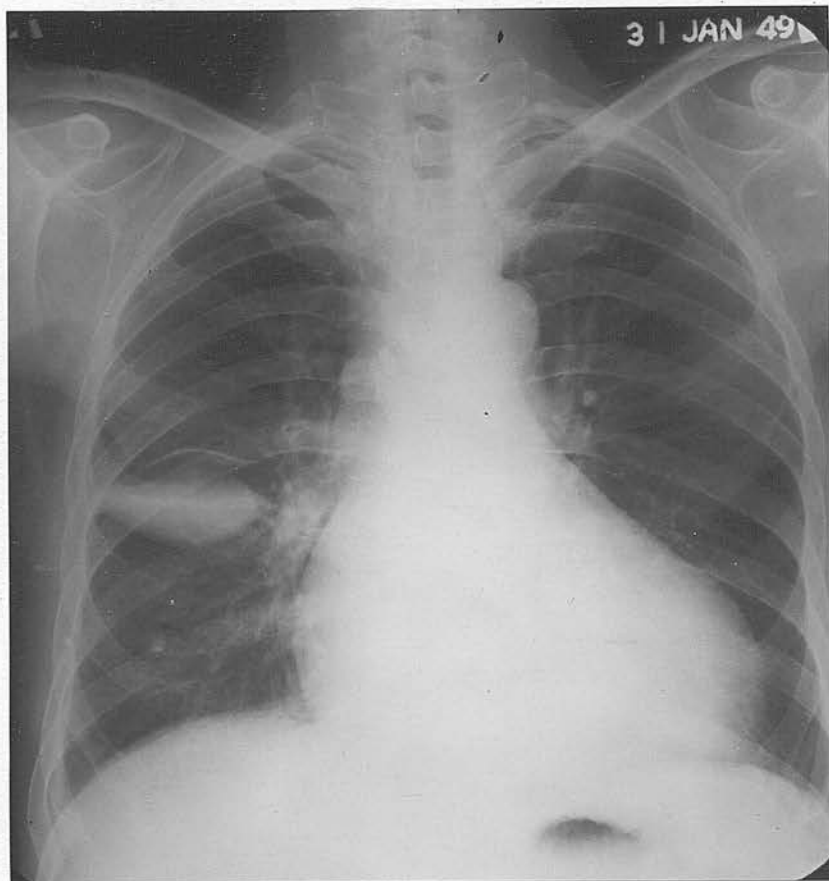


Fig. 59. Case 3.

Chest X-ray on 31. 1.49 following treatment with digitalis and mersalyl. The fluid in the costophrenic angles has disappeared and the interlobar effusion is much reduced. There is little evidence of lung congestion.

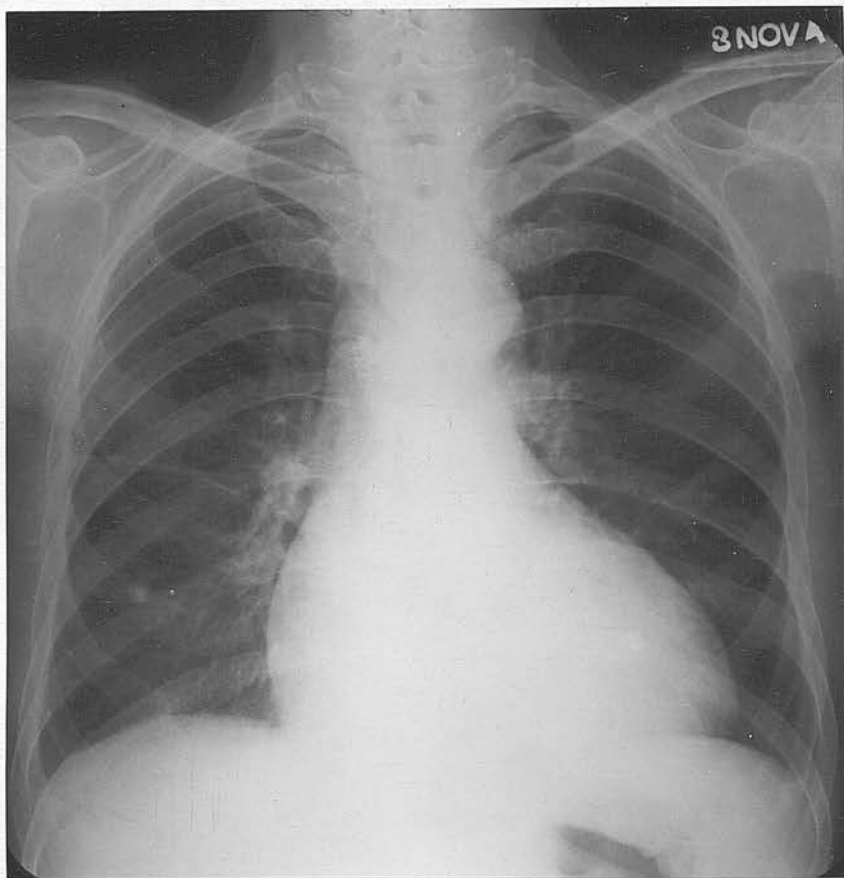


Fig. 60. Case 3.

Chest X-ray on 3.11.49. By this time the patient had resumed his normal activities and had no symptoms. Cardiac enlargement is still present. The site of the interlobar effusion is represented by slight thickening of the interlobar fissure.

effusion with small additional effusions in both costophrenic angles and general vascular congestion in the lungs. A tentative diagnosis of early left-sided cardiac failure was made. The patient was asked to rest in bed at home.

He reported on 11. 1.49. The dyspnoea was now more troublesome. Clinical examination revealed deterioration in his condition. The pulse was irregular; the neck veins were distended; the liver was palpable two inches below the costal margin; there was pitting oedema of the ankles and some ascites. It was now clear that the left-sided failure had gone on to congestive failure. The urine contained no sugar or albumin. An X-ray of chest showed no change from Fig. 58. An E.C.G. showed slow auricular fibrillation with evidences of an old apical infarct. Estimation of plasma proteins gave albumin 3.9 Gms. and globulin 2.0 Gms. per 100 mils..

A diagnosis of cardiac failure secondary to old myocardial infarction and fibrosis was made. Treatment in hospital with digitalis and mersalyl resulted in rapid improvement. An X-ray of chest (Fig. 59) three weeks later showed disappearance of the fluid in the costo-phrenic angles and lessening of the interlobar effusion. At this time, a second diagnostic aspiration of the interlobar fluid again gave the features of a transudate. After the initial rapid improvement progress was slow, and some oedema of the ankles and enlargement of the liver persisted despite intensive therapy. These features were still present when he was discharged two months later. Administration of digitalis and mersalyl was continued at home.

He reported again in November, 1949. He was now symptom free and had no signs of cardiac failure although slow auricular fibrillation was still present. An X-ray of chest (Fig. 60) showed that the interlobar effusion had disappeared, leaving some thickening of the interlobar fissure; cardiac enlargement was still present.

Comment. A man aged 68 presented with vague ill-health and was found on radiological examination to have an interlobar pleural effusion between the upper and middle lobes on the right side. On aspiration this proved to be a transudate. No apparent symptoms or signs of cardiac failure were present. In the next two months he developed undoubted cardiac

failure with auricular fibrillation due to old myocardial infarction and fibrosis. Treatment resulted in resolution of the cardiac failure and the interlobar transudate. In this patient, an interlobar transudate was the presenting sign of left-sided, and later, congestive cardiac failure.

Case 4. A female patient aged 51 was admitted to hospital on 22. 3.49. For some months she had complained of cough, slight dyspnoea on exertion and easy fatigue; one week before admission she had coughed up a small quantity of bright red blood - red streaking of sputum continued the next day. The dyspnoea had been worse since the haemoptysis, being particularly troublesome during the night. Previous medical history was essentially negative. On examination, she was obviously dyspnoeic; there was a moderately large left pleural effusion; the left ventricle was clinically enlarged with B.P. 135/100, but otherwise the cardio-vascular system seemed normal. Diagnostic aspiration revealed haemorrhagic fluid which clotted on standing and was sterile on culture; the Pathologist reported the presence of numerous malignant cells.

The whole picture seemed typical of inoperable bronchial carcinoma. The Physician-in-charge decided that further investigation was not indicated. After a period of rest in bed with therapeutic aspirations she was discharged i.s.q. on 30. 5.49. It was noted at the time that her condition had not deteriorated as rapidly as might have been expected in the circumstances. An X-ray of chest shortly before her discharge showed a left pleural effusion and enlargement of the left ventricle without evidence of congestive or other changes in the lung fields.

She was admitted to another hospital in January, 1950, that is six months later. The only significant change in the clinical picture was that the left pleural effusion was no longer blood-stained - the fluid was not examined beyond naked-eye inspection. A chest X-ray (Fig. 61) again showed a left pleural effusion with left ventricular enlargement, but without significant pulmonary congestion. It was felt at this time that the fluid might be cardiac in origin since the original diagnosis of bronchial carcinoma seemed untenable. The enlargement of the left ventricle was attributed to mild hypertension. An E.C.G. showed only left axis deviation.

Treatment with digitalis and mersalyl led to

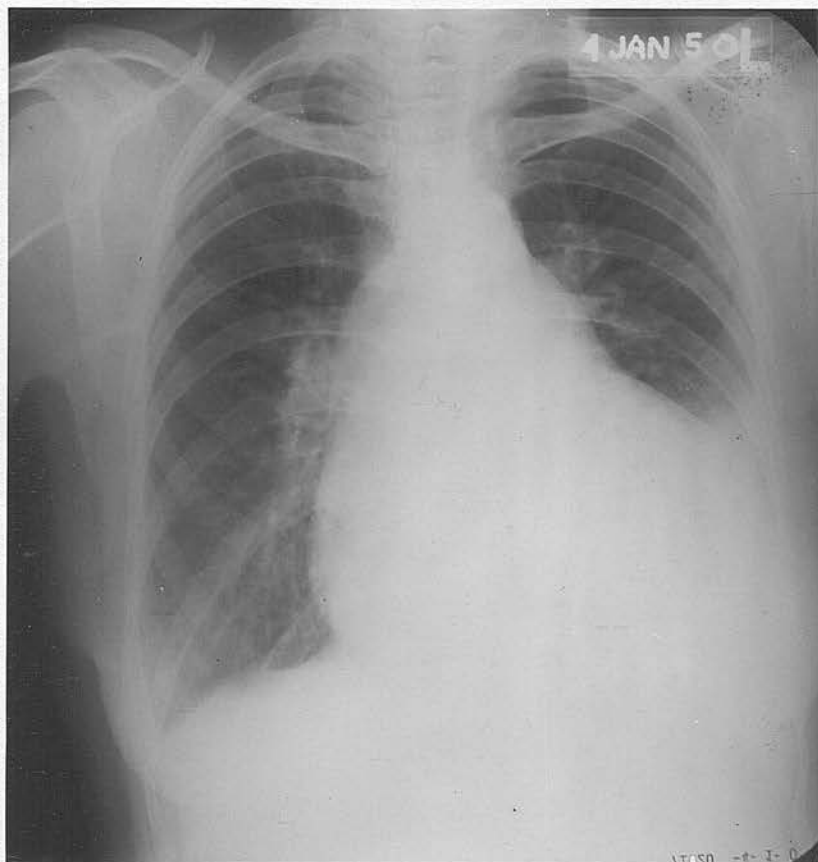


Fig. 61. Case 4.

Chest X-ray on 4. 1.50 showing a left pleural effusion with cardiac enlargement, mainly of the left ventricle. The lung fields show remarkably little congestion. At the time of this X-ray, the fluid had already been present for 9 months.

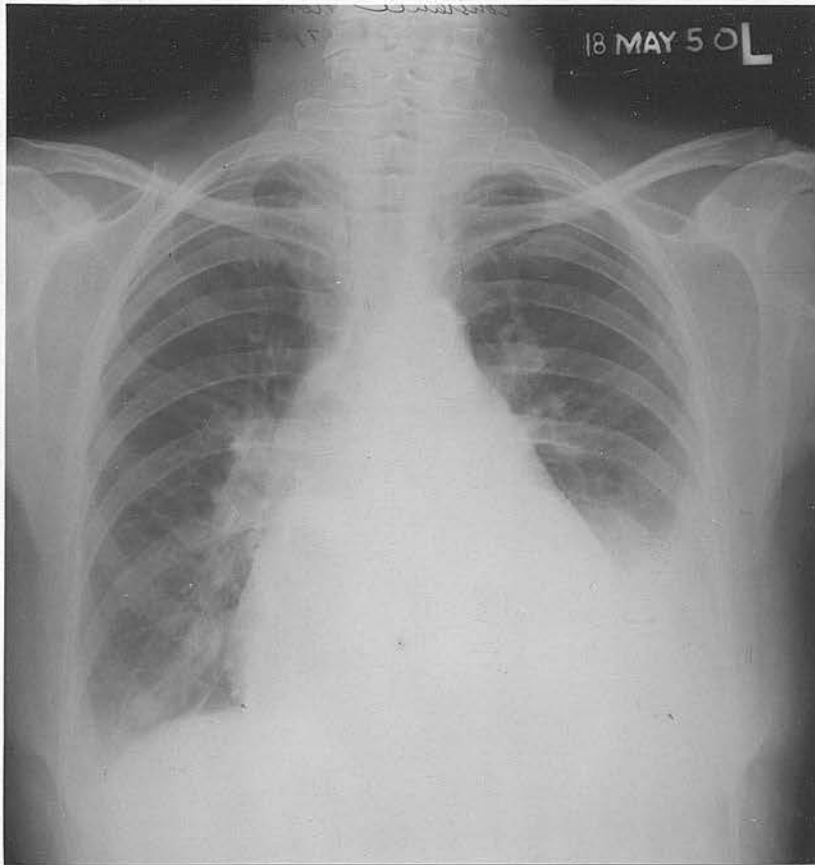


Fig. 62. Case 4.

Chest X-ray on 18. 5.50 showing remarkably little change over the preceding 5 months during which the patient was treated with digitalis and mersalyl. There is probably some diminution in the quantity of fluid. The improvement referred to in the text was clinical rather than radiological.

clinical improvement over the next 5 months. A chest X-ray in May, 1950, (Fig. 62) showed some diminution of heart size and in the quantity of fluid, neither change, however, being particularly marked. In June, 1950, she reverted to the care of her family doctor.

In February, 1951, she was admitted to yet another hospital in great respiratory distress. Death occurred some after admission. Necropsy showed the following

i. Rheumatic aortic incompetence with hypertrophy and dilatation of the left ventricle.

ii. Gross pulmonary oedema from left ventricular failure.

iii. A large collection of clear fluid in the left pleural cavity with compression of the left lower lobe.

iv. No fluid in the right pleural cavity, although no adhesions were present.

Comment. The most important feature is the remarkable chronicity, over a period of nearly 2 years, of a unilateral left pleural transudate due to left ventricular failure. At no time, despite a free right pleural cavity, was there a right-sided transudate, and not until immediately prior to death was there evidence of significant pulmonary oedema. Although it was known from the beginning that the left ventricle was enlarged, the cause of this was not correctly determined clinically, and, in any event, there seemed little connection, at least initially, between the enlargement and her clinical state. The original diagnosis of bronchial carcinoma, even in retrospect, seems reasonable in view of the history, haemoptysis, haemorrhagic fluid and the finding in the fluid of so-called malignant cells. It should

be noted that, at necropsy, clear pleural fluid was still present without evidence of pulmonary infarction; this is emphasised, since it might with justification be argued that the original haemorrhagic effusion was due to pulmonary infarction, which would also explain the haemoptysis. On the whole, however, it seems probable that the continuation of the fluid was due to transudation, an argument supported by the partial response to cardiac therapy.

Case 5. A male patient aged 46 developed a left pleural effusion following operative closure of a perforated duodenal ulcer on 13. 1.51. This was regarded by the surgeon as simple inflammatory in origin. Following treatment with penicillin and chloramphenicol, he was discharged from hospital, although his general health was far from satisfactory. On attempting to resume work, he found that he was extremely breathless on exertion. He was re-admitted to a medical ward on 4. 3.51.

On examination, he was obviously dyspnoeic; there was a moderately large left pleural effusion with numerous crepitations throughout both lungs. B.P. was 90/70. X-ray of chest on 5. 3.51 (Fig. 63) showed a left pleural effusion with changes in both lung fields which were thought by the radiologist to be either inflammatory in origin or due to infiltration of the lymphatics. Diagnostic aspiration revealed a clear serous fluid which was sterile on culture and contained mainly serosal cells; protein content was 1.8 Gms. per 100 mils..

Up to this point, the information from the surgical side had been allowed to weigh too heavily in favour of a simple inflammatory condition. A review of the case strongly suggested a cardiac cause. An E.C.G. showed evidence of an apical myocardial infarction corresponding in age to the date of his original operation. Treatment with digitalis and mersalyl led to dramatic improvement. X-ray of chest on 14. 3.51 (Fig. 64) showed almost complete disappearance of the left pleural effusion and congestive - not inflammatory - changes in the lung fields.

Comment. This patient obviously suffered a "silent" myocardial infarction at the time of his operation.



Fig. 63. Case 5.

Chest X-ray on 5. 3.51 showing left pleural effusion, obscured cardiac contour and wide-spread changes in both lung fields. It is obvious that the lung changes are congestive in nature, but, at the time, inflammation and lymphatic infiltration were seriously considered.

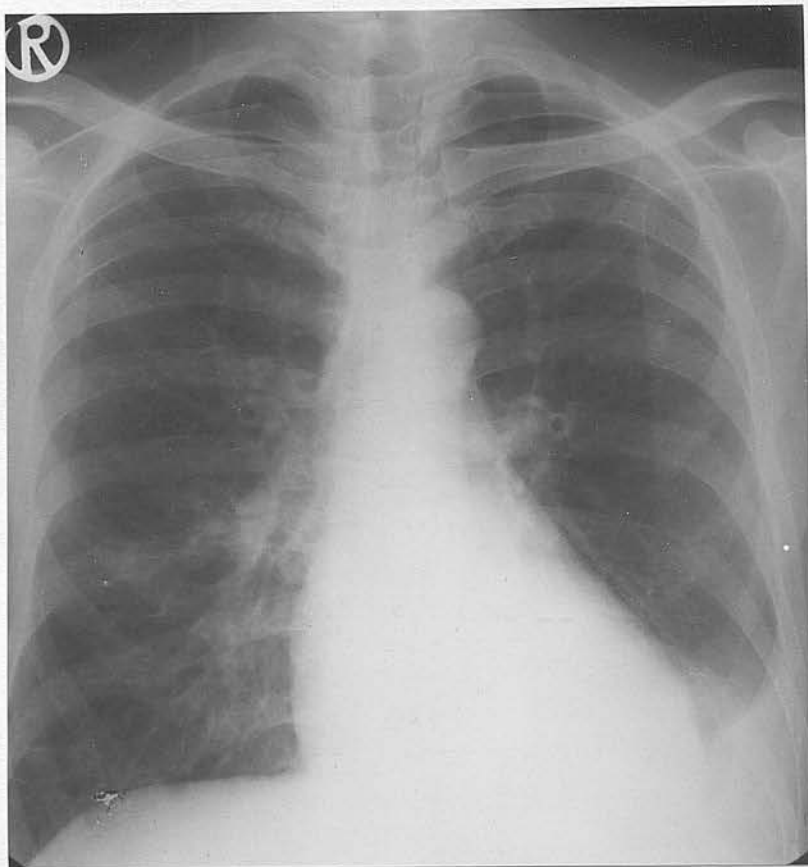


Fig. 64. Case 5.

Chest X-ray on 14. 3.51 following treatment with digitalis and mersalyl. The left pleural effusion has largely absorbed and the lung fields are clear. The heart may be slightly enlarged.

In retrospect, no great problem in diagnosis existed, although the history was misleading. The value of E.C.G. is emphasised.

DISCUSSION.

Five "difficult" cases have been presented in some detail to show that, in unusual circumstances, cardiac pleural transudate may escape early recognition with possible failure of institution of effective therapy. From the clinical point of view, it seems that the first essential in the diagnosis of cardiac transudate is simply to remember its existence; thereafter the problems, as shown in the cases described, become less formidable. Further help in diagnosis may be obtained from an appreciation of the following points:-

(a) History.

As might be expected in cardiac transudate, none of the 5 patients complained of pleuritic pain; unfortunately, from the diagnostic point of view, neoplastic effusion (see page 214) is also commonly not preceded by pleuritic pain. 4 of the 5 complained of dyspnoea, but in only 1 was the dyspnoea suggestive of left ventricular failure, being worse during the night. There was a tendency for the dyspnoea to be greater in degree than could be accounted for by the mere presence of the pleural effusion; again this may be a feature of neoplasm.

On the whole, the history, especially in the cases of myocardial infarction, was singularly unhelpful in suggesting the correct diagnosis.

(b) Type of Cardiac Lesion.

In all 5 cases, the pleural transudate was present, at least initially, without evidence of systemic congestion. As Bedford and Lovibond (1941) have pointed out, pleural transudate precedes systemic congestion only in left heart failure, of which the important causes are hypertension, myocardial infarction and aortic valvular disease. The importance of a complete E.C.G. examination in the detection of silent myocardial infarction was emphasised in 3 of the 5 cases.

(c) Age of Patient.

All 5 patients were over 40 years of age. This is in keeping with the fact that left heart failure is uncommon in younger patients, in whom systemic congestion, due to right heart failure, precedes pleural transudate, thus eliminating difficulty in diagnosis. It would seem wise to consider a cardiac lesion causing left-sided failure in any patient over 40 years of age presenting with a pleural effusion.

(d) Associated Pulmonary Oedema.

It is disturbing to note that in only case 5 was there clinical evidence, in the form of crepitations, of associated pulmonary oedema. Since it is generally accepted - Bedford and Lovibond (1941) - that cardiac pleural transudate is secondary to pulmonary

engorgement and oedema, it is difficult to explain the absence of crepitations, save by the assumption that the oedematous fluid is mainly interstitial in the framework of the lung. Whatever the explanation, it is clear that the absence of crepitations does not exclude a diagnosis of pleural transudate due to left ventricular failure.

The chest X-ray is of much greater value - cases 1, 3 and 5 - in demonstrating pulmonary engorgement. In this connection, considerable care is required in interpreting lung changes which may be present; the appearances of pulmonary engorgement and oedema vary from case to case, and there may be a tendency among radiologists - e.g. case 5 - to diagnose, in error, simple inflammation or even lymphangitic carcinoma. The Physician, with the advantage of the clinical picture before him, is better equipped than the radiologist to assess such changes. A further point of difficulty is that the lungs may not show appreciable radiological evidence of engorgement - case 4; again this is hard to explain, although in case 4 it was not possible to exclude a small pulmonary infarction as the precipitating cause of the pleural fluid. Cardiac enlargement may also be noted on the chest X-ray - cases 1, 3 and 4; in older people, this is not an uncommon finding in pleural effusion due to causes other than cardiac failure, and therefore it is not of much diagnostic value.

(e) Side of Effusion.

In none of the 5 cases was the pleural fluid

initially bilateral; in 3 it was on the left side and in 2 it was on the right side. It is clear that in a difficult case, no reliance can be placed on the text-book description of cardiac transudate, viz. often bilateral; if unilateral, usually on the right side.

(f) Examination of the Pleural Fluid.

In case 4, the fluid was haemorrhagic; this is an unexpected finding in cardiac transudate; apart from bleeding due to the puncture of the chest, associated pulmonary infarction may cause a haemorrhagic effusion.

Cytological examination has already been discussed in detail (Section II). In summary, a cardiac transudate may have either lymphocytes or serosal cells predominant; there is a tendency for the Pathologist to diagnose malignant cells in error (e.g. case 4).

The protein content of a cardiac transudate has always given rise to discussion and speculation. In 1 of the 5 cases, the protein was unfortunately not estimated, but it was probably high since the fluid clotted on standing. In 3, the protein was less than 2 Gms. per 100 mils.; in 1, the protein was 2.9 Gms. per 100 mils.. Bedford and Lovibond (1941) found that in 27 cardiac transudates, the protein varied from 0.6 Gms. to 4.2 Gms. per 100 mils., the average being 2.1 Gms. per 100 mils.. They comment

on the fact that the higher figures overlap those of exudates, and attribute this to mild chronic inflammation in the congested underlying lung. It is clear that the protein in a cardiac transudate is not always low enough to suggest the correct diagnosis. Conversely, a low protein may rarely occur in inflammatory and malignant fluids. Of 72 tuberculous and other inflammatory fluids examined by the author, 2 had a protein content of less than 3 Gms. per 100 mils., while of 21 malignant fluids, 1 had a protein content of less than 3 Gms. per 100 mils.. On the other hand, only 1 of those 3 unusually low proteins was less than 2 Gms. per 100 mils.. It may be stated that a protein of less than 2 Gms. per 100 mils. is highly suggestive of transudate, but even so, the occasional exception causes difficulty in assessing the individual case.

(g) Therapeutic Test.

In 3 of the 5 cases, the response, clinically and radiologically, to digitalis and diuretic therapy, was little short of dramatic, and emphasises the value to the patient of correct diagnosis. In 1 case (case 4) the response was less marked, the transudate remaining i.s.q. for nearly 2 years. Bedford and Lovibond (1941) have commented on this occasional remarkable chronicity of pleural transudate due to left ventricular failure. In the remaining case (case 2), death took place before the

diagnosis was established.

In a difficult case, a good response to cardiac therapy is the ultimate proof of the diagnosis. It is therefore suggested that if a suspicion of cardiac transudate exists, a trial of such therapy should be given over a limited period of (say) 5 days. It is better to manage the patient in this way rather than to arrange premature bronchoscopy and thoracoscopy in the search for possible and almost certainly untreatable malignant disease.

Interlobar Transudate in Cardiac Failure

Case 3, in whom an interlobar transudate was the presenting sign of left-sided, and later, congestive cardiac failure, is of such interest and importance that further discussion on this problem is indicated.

A. Cases in the Literature.

Including case 3 described above, 36 cases of cardiac interlobar transudate have been reported - Helm (1917), Fleischner (1926), Stewart (1928), Kiser (1929), Freedman (1931), Steele (1932), Vesell (1932), Austrian (1932), Stein and Schwedel (1934), Shiflett (1935), Levitin (1937), Bedford and Lovibond (1941), Russakoff and Weinberg (1944), Robertson (1951). The 36 cases are analysed in the following tables.

TABLE 22 /

TABLE 22Site of Interlobar Transudate

Site	No. of Cases
Right Lesser Fissure	22
Right Greater Fissure	3
Right Lesser and Greater Fissures	2
Left Interlobar Fissure	2
Not Stated	7
TOTAL	36

TABLE 23Incidence and Site of Accompanying Effusion in General Pleural Cavity

Incidence and Site	No. of Cases
No Accompanying Effusion	14
Effusion in Right Pleural Cavity	7
Effusion in Left Pleural Cavity	8
Effusion in Both Pleural Cavities	0
Not Stated	7
TOTAL	36

TABLE 24 /

TABLE 24Aetiology of Cardiac Disease causing
Interlobar Transudate

<u>Aetiology</u>	<u>No. of Cases</u>
Aortic Valve Disease	6
Hypertension	6
Coronary Occlusion	6
Arteriosclerosis	5
Myocardial Fibrosis	3
Thyrototoxicosis	1
Not Stated	9
TOTAL	36

TABLE 25Age Incidence of Interlobar Transudate
in Cardiac Failure

<u>Age Group (Years)</u>	<u>No. of Cases</u>
Over 50	21
40 - 50	2
30 - 40	4
20 - 30	1
Not Stated	8
TOTAL	36

Tables 22 - 25 indicate that interlobar transudate occurs mainly in the right lesser fissure; that it may or may not be accompanied by effusion

into the general pleural cavities; that the aetiology of the cardiac failure is a condition causing either left-sided or simultaneous left- and right-sided failure - the conditions causing right-sided failure alone, for example tricuspid valvular disease and chronic lung disease, are not mentioned by any author; that, in accordance with the role played by hypertension, arteriosclerosis and coronary artery disease in aetiology, the main incidence is in the older age groups.

B. Problems in Diagnosis.

In 14 of the 36 cases, there was no accompanying effusion into the general pleural cavities. In such circumstances, the correct diagnosis may not be thought of at first because of its rarity. Tuberculous loculated pleural effusion, loculated empyema or even neoplasm may be wrongly diagnosed. A patient with coronary occlusion, which is a common cause of cardiac interlobar transudate, may have fever, cough, chest pain and leucocytosis, all of which may suggest empyema.

A cardiac interlobar transudate, however, usually occurs in patients over 40 years of age, when tuberculous effusions are less common. The fluid, on examination, has the characteristics of a transudate. A cardiac condition causing left- or simultaneous left- and right-sided failure is present.

Radiologically, the fluid is in most cases localised in the right lesser fissure and tends to disappear with treatment of the cardiac failure and to re-appear with relapse; the lung fields tend to show hilar and basal congestion due to associated pulmonary oedema; the cardiac shadow, especially the left ventricle, is usually enlarged.

C. Mode of Production of Interlobar Transudate.

It is necessary to consider first how transudates are formed in the general pleural cavities in cardiac failure. Pulmonary infarction along a pleural surface may be an occasional cause, but in this the fluid, strictly speaking, is an exudate rather than a transudate. Bedford, Papp and Parkinson (1941) consider that true hydrothorax is a result of stasis in the pulmonary circulation with transudation from the visceral pleura due to left ventricular failure. They point out if hydrothorax were mainly due to systemic stasis we should expect to find it early and constantly in conditions of right heart failure with severe venous engorgement, for example, in tricuspid stenosis. On the contrary, in this condition, pulmonary oedema and hydrothorax are absent, but ascites is common. Doubtless those general principles apply also to interlobar hydrothorax; indeed it has been shown above that left-sided failure or simultaneous left- and right-sided failure, as opposed to pure right-sided failure, is

the important factor in all cases.

The localisation in an interlobar fissure, however, is not always easy to explain. In some cases - Helm (1917), Steele (1932), Austrian (1932), Levitin (1937) and Russakoff and Weinberg (1944) - necropsy has shown that fibrous obliteration of the general pleural cavities has left no space other than an interlobar fissure, nearly always the right lesser, in which the fluid could accumulate. In this connection, Laennec described an instance of hydrothorax limited by an antecedent obliterative pleurisy to the lower half of the right thoracic cavity in a patient who had died of myocardial disease. Bedford and Lovibond (1941) found that in 132 necropsied cases of cardiac failure, complete obliteration of one or both pleural cavities occurred nine times. They point out that the obliterative pleurisy in such cases may be due to repeated pleural reactions associated with vascular congestion rather than to previous tuberculous or simple inflammatory conditions; indeed a previous history of chest disease is rare.

In many other cases, radiological or necropsy evidence of associated fluid in the general pleural cavities indicates that previous obliterative pleurisy is not the only explanation. In those cases, Bedford (1939) suggests that, since hydrothorax is due to transudation from the visceral pleura, the

interlobar area will have the benefit of two trans-
udating surfaces as opposed to the general pleural
space which has only one. Rigler (1936) has a
simpler explanation, namely that fluid may seep into
an interlobar fissure from a collection in the
general pleural space. This may frequently be
observed during screening. Later a pleural re-
action may seal off the communicating channel be-
tween the fissure and the general pleural space
without causing a generalised obliterative pleurisy.

SECTION VIPLEURAL EFFUSION IN THE COLLAGEN DISEASES

In recent years, and especially since the discovery of the therapeutic effects of A.C.T.H. and cortisone, it has become customary to group, under the term "collagen diseases", the following conditions - acute disseminated lupus erythematosus, rheumatoid arthritis, acute rheumatic fever, scleroderma and periarteritis nodosa. In this section observations pertaining to the occurrence of pleural effusion in those conditions are presented.

Acute Disseminated Lupus Erythematosus

Acute disseminated lupus erythematosus has a clinical picture characterised by prolonged irregular fever, arthritis sometimes becoming deforming, moderate general lymphadenopathy, moderate splenomegaly, inflammation of the serous membranes, frequently a skin lesion of the nature of lupus erythematosus, sometimes a verrucous endocarditis, almost invariably leucopaenia, and very often a renal lesion causing albuminuria and renal insufficiency. The disease often has a course of wave-like intensity with intermediate periods during which the symptoms and signs are in abeyance. Finally, 95% of cases occur in women of the child-bearing age.

Unfortunately for the clinician, the complete clinical picture is seldom present, and, especially

in the absence of a typical butterfly skin eruption, difficulties in diagnosis may arise. Baehr and Pollack (1947) have found that rheumatic fever and rheumatoid arthritis are the most common misdiagnoses. Occasionally the disease remains undiagnosed until necropsy, having been during life a baffling "pyrexia of unknown origin"; in such cases it is not surprising that tuberculosis is often given as the provisional diagnosis by the clinician to the Pathologist. In this connection it is interesting to note that Boeck (1900) believed that the disease was tuberculous in origin, a belief which was not shaken until the publication of a paper by Kiel (1933).

The following case report illustrates how tuberculosis, in particular tuberculous pleurisy with effusion, may be simulated:-

Case 1. A female patient aged 40 was first admitted to hospital on 10. 2.48. For the previous 18 months she had complained of vague aches in numerous joints; 10 days before admission she developed acute LEFT pleurisy with a high temperature; the temperature had subsided prior to admission; 5 days after admission she developed an acute RIGHT pleurisy, again with a high temperature (Fig. 65); the right pleurisy went on to effusion, the fluid being clear and serous, sterile on culture and with a lymphocytic exudate. A chest X-ray at this time (Fig. 66) showed only a right pleural effusion. She remained in hospital for seven weeks, during which time the pyrexia subsided gradually and the effusion absorbed. There was nothing in the clinical picture to suggest a diagnosis other than tuberculous pleurisy with effusion, although the history of vague joint pains and the onset with consecutive left and right pleurisies were considered a little unusual.

The patient was not seen again until 7. 6.49, that is more than a year later. She had kept well during that time, apart from mild dyspnoea on exertion, but three weeks before had developed fever with

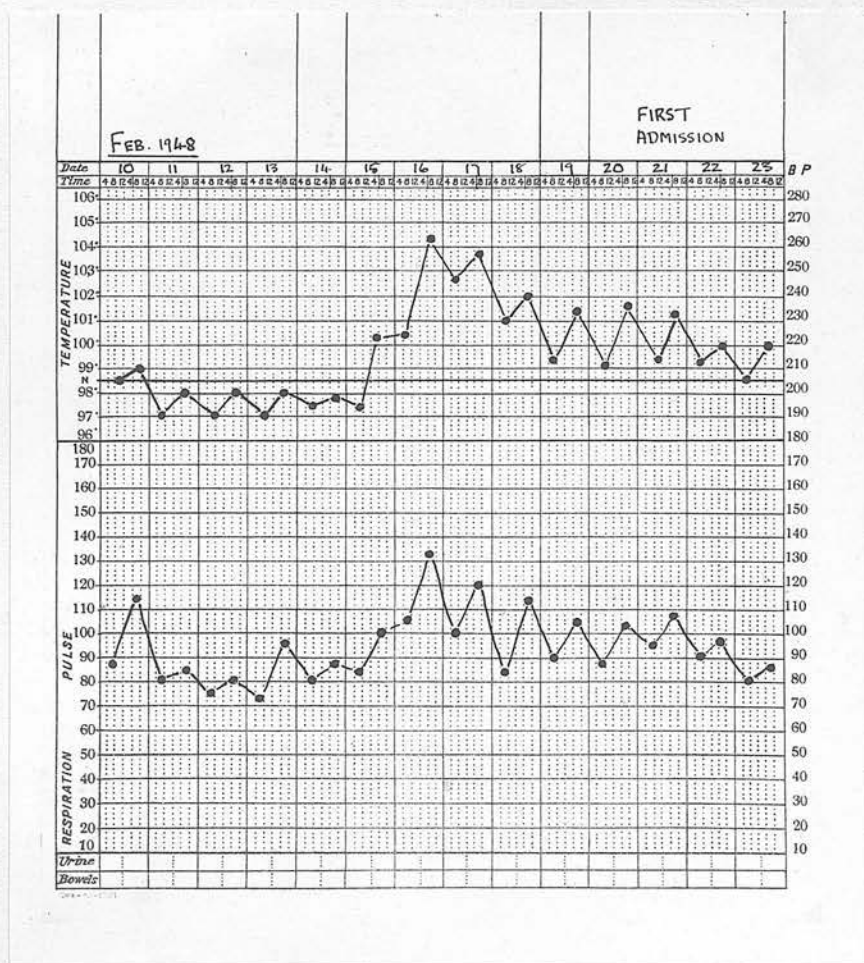


Fig. 65. Case 1.

Brisk pyrexial reaction to acute right pleurisy 5 days after admission. The pyrexia of the previous acute left pleurisy had subsided prior to admission. "Waves" of pyrexia are common in acute disseminated lupus erythematosus.



Fig. 66. Case 1.

Chest X-ray following partial aspiration of right pleural effusion. There is no evidence of intra-pulmonary or cardiac disease. The diagnosis at this time was primary tuberculous pleurisy with effusion - consecutive left and right.

bilateral pleuritic pain and once again vague pains in her joints. Admission to hospital was arranged. Clinical examination was negative apart from slight dullness at both lung bases, and X-ray of chest confirmed the presence of small effusions in both pleural cavities. Aspiration of the fluid was not attempted. On this occasion she was in the ward for five weeks, during which time there was no pyrexia; both effusions absorbed completely, the only disquieting feature on discharge being a persistently high E.S.R., 48 mm. in 1 hour. At this point it was considered that the course of the illness was unusual for a tuberculous pleurisy, but no alternative diagnosis came readily to mind.

She kept well for a further two months, but was admitted for a third time on 27. 9.49 with a high temperature and extreme tachycardia (Fig. 67). On this occasion there was no pleural effusion. Death occurred in coma after 3 days. The provisional clinical diagnosis was miliary tuberculosis, but necropsy showed the following features pathognomonic of acute disseminated lupus erythematosus.

1. Atypical verrucous (Libman-Sacks) endocarditis affecting the tricuspid valve.
2. Pericarditis with focal collagen degeneration.
3. Focal myocarditis with arteriolitis.
4. Periarteriolar fibrosis in spleen.
5. Fibrinoid degeneration of the renal glomerular capillaries, giving the "wire-loop" appearance.

It was hoped that the pleura might show characteristic changes, but both pleural cavities were obliterated by fibrosis, and microscopical examination showed only non-specific fibrosis. The lungs showed only terminal broncho-pneumonia. There was no evidence of any form of tuberculosis.

Comment. This case demonstrates conclusively that disseminated lupus can begin with an episode of febrile pleurisy progressing to effusion in a manner identical with a primary tuberculous pleurisy with effusion. The history of vague joint pains for 18 months prior to the acute illness is not necessarily against a diagnosis of tuberculosis, since the

disease entity of "tuberculous rheumatism" has long been known or suspected to exist - Poncet and Le Riche (1909); Sheldon (1946). Cameron (1952) has been struck by the fact that tuberculous patients often have a previous history of "rheumatic fever", and yet they show no evidence of cardiac damage and the description of painful joints is not that of the inflamed intensely painful joints of acute rheumatism. Poncet and Le Riche describe three clinical forms of tuberculous rheumatism, any of which may occur either prior to or along with an active tuberculous infection. Those forms are

1. Arthralgia of many joints without redness, swelling or heat.
2. Acute arthritis simulating rheumatic fever.
3. Chronic arthritis simulating rheumatoid arthritis.

The present patient, who never showed abnormality of the joints on clinical examination, having only vague pains (arthralgia), could easily have been included in the first category, that is if the concept of tuberculous rheumatism is to be accepted at all. Its existence is accepted by no less an authority than Sheldon (1946) who has described several cases in children. He states, however, that it is rare in children, and it must be even more rare in adults. It would seem wise, when presented with acute febrile pleurisy and arthralgia in an adult, especially a female adult, to think of a tuberculous aetiology, but at the same time to observe closely

for the other manifestations of disseminated lupus. The same argument applies even when there is swelling or other deformity of the joints - i.e. more than mere arthralgia, because such changes certainly occur in disseminated lupus, and also, according to Poncet and Le Riche, in tuberculous rheumatism.

Further comment is required on the fact that the present patient had an acute febrile left pleurisy prior to admission followed by an acute febrile right pleurisy with effusion after admission. This sequence of events is compatible with a tuberculous aetiology, but there is no doubt that it is uncommon for the ordinary primary tuberculous pleurisy to be either simultaneously or consecutively bilateral. It is also uncommon for tuberculous pleurisy, in the absence of overt pulmonary tuberculosis, to recur after a long interval of time; the present patient had a recurrence of bilateral pleurisy with small effusions after an interval of more than a year. In retrospect, it is easy to incriminate disseminated lupus as a cause of those phenomena, since the disease involves collagen tissue throughout the body and is therefore likely to attack the pleura on both sides, and it is also known to pursue a wave-like course with recurrent involvement of organs at often widely separated intervals. Tremaine (1934) describes a case appropriate to this discussion:-

"Throughout the four months the patient remained in hospital there were frequent bouts of fever,

chills and joint pains. The physical signs of a small amount of fluid at the bases of both lungs were usually present. A right thoracentesis revealed 75 c.cs. of fluid but no organisms."

From those observations, it is clear that disseminated lupus should be suspected in a patient with bilateral - simultaneous or consecutive - acute febrile pleurisy, with or without effusion, especially if the pleurisy pursues a wave-like course with recurrence. If the patient is a female, the suspicion would naturally be greater. In this type of case, as in the type with acute febrile pleurisy and arthralgia or arthritis, observation for the other features of disseminated lupus is required, including search for the lupus erythematosus (L.E.) cell in the sternal marrow and possibly, if presumptive evidence of lupus exists, a therapeutic trial with cortisone or A.C.T.H.. At the same time, unusual forms of tuberculosis must be kept in mind and appropriate search made for the tubercle bacillus in the pleural fluid and fasting gastric juice or sputum. The character of the pleural fluid, other than the possible finding of the tubercle bacillus, does not help in differential diagnosis, since both tuberculosis and disseminated lupus give a clear, serous, lymphocytic fluid.

Finally it should be emphasised that the foregoing discussion applies mainly to pleurisy and pleural effusion occurring during the early stages of

disseminated lupus. In the later stages of the established disease, pleurisy and pleural effusion may sometimes be due to a complicating bronchopneumonia or to cardiac failure secondary to endocardial, myocardial or pericardial lesions. It is even possible that coincidental quiescent pulmonary tuberculosis might be reactivated with subsequent pleural involvement. In the case described there was no doubt about the absence of those complications at the time of the original pleurisy. Klemperer, Pollack and Baehr (1941), in a series of 35 autopsied cases of disseminated lupus, found that the pleura in cases uncomplicated by bronchopneumonia or cardiac failure had a typical gelatinous appearance with microscopical evidence of fibrinoid degeneration of the collagen.

Rheumatoid Arthritis

There is no doubt that pleurisy and pleural effusion can occur during the course of rheumatoid arthritis, but it has always been a matter of dispute whether the pleural involvement is due to the rheumatoid arthritis or whether it is due to complicating or coincidental pulmonary diseases such as bronchiectasis or tuberculosis. For purposes of argument, it seems reasonable to assume that the pleura can be primarily involved, since the disease is essentially systemic in nature, although the most obvious lesions are in the joints. From time to

time clinicians and pathologists have drawn attention to the occurrence, in rheumatoid patients, of iritis, scleritis, cardiac lesions, lesions of the muscles, splenomegaly, lymphadenopathy, subcutaneous nodules, peripheral neuritis and even - Ellman and Ball (1948) - an unusual type of chronic fibrosing interstitial pneumonitis. In the midst of those diverse and widespread systemic lesions, the pleura has received scant attention, at least from clinicians, although some information is supplied by pathologists. Fingerman and Andrus (1943), in a study of 61 autopsied cases of rheumatoid arthritis, found obliterative pleuritis in 23 cases, in the majority of which there was no obvious lung pathology to account for the changes. Similarly, Rosenberg, Baggenstoss and Hench (1944), in a series of 30 autopsied cases, found fibrous adhesions between the visceral and parietal pleura in 22 cases, although in 14 of those there was also evidence of active or healed pulmonary tuberculosis. Both groups of authors conclude that rheumatoid arthritis can be responsible for recurrent pleuritis leading to fibrous changes.

The following case reports illustrate some of the clinical problems which may arise.

Case 2. A female patient aged 42 first came under observation in October, 1950. Six months previously she had suffered from an episode of acute left-sided pleurisy followed in one week by swelling and stiffness of the small joints of the hands; subsequently pain and stiffness developed in both knees, both ankles, both elbows and the left wrist. On clinical examination, she had typical rheumatoid changes in the fingers with muscular wasting; there was also

a small left pleural effusion. E.S.R. was 98 mm. in 1 hour. Left thoracentesis gave a clear, serous fluid with lymphocytic exudate; the fluid was sterile on ordinary culture and failed to grow tubercle bacilli on Lowenstein-Jensen culture. X-ray of chest at this time (Fig. 68) showed nothing more than the left pleural effusion.

With rest in bed, her condition gradually improved, but in December, 1950, there was an exacerbation of joint pain and stiffness with acute right-sided pleurisy which progressed to a small effusion. Right thoracentesis revealed fluid similar to that on the left. In the next 3 months, there was again gradual improvement with fall in the E.S.R. to 6 mm. in 1 hour. The pleural effusions, however, showed remarkable chronicity, being still obvious on a chest X-ray in March, 1951 (Fig. 69). She has kept well since March, 1951, but has persistent rheumatoid deformity of the hands and residual dullness at both lung bases.

Comment. There can be little doubt about the diagnosis of rheumatoid arthritis in this patient. The first manifestation of the disease seemed to be a left pleurisy proceeding to effusion. The right pleurisy with effusion coincided with an exacerbation of the joint pains. Both effusions showed remarkable chronicity akin to the joint lesions. There was no clinical or radiological evidence of underlying pulmonary disease and the whole course was most unlike that of a primary tuberculous condition. It must be admitted, however, that "tuberculous rheumatism" is a possibility - type 3 of Poncet and Le Riche.

Case 3. A female patient aged 51 was admitted to hospital on 20. 6.51. During the previous year she had noticed the gradual development of pain and stiffness in the knees, shoulders, wrists and the small joints of the hands. Immediately prior to admission she had developed acute right-sided pleurisy with fever and dyspnoea. Clinical examination showed typical rheumatoid changes in the hands, with "spindling", muscular wasting and ulnar

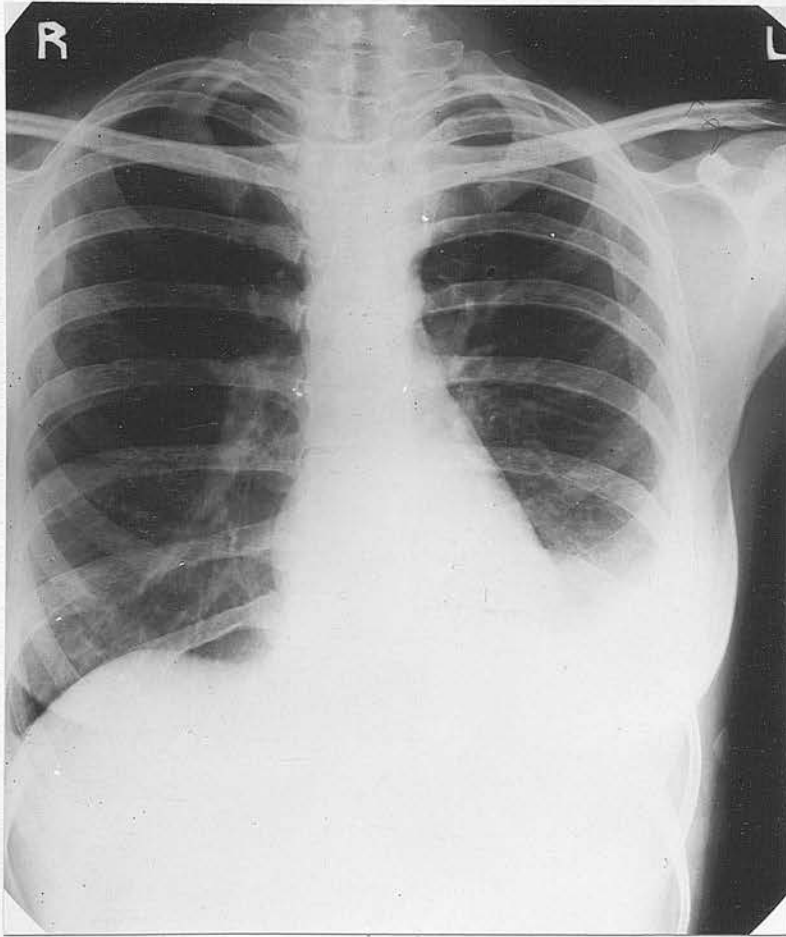


Fig. 68. Case 2.

Chest X-ray six months after onset of rheumatoid arthritis preceded by acute left pleurisy. A left pleural effusion is present. There is no evidence of intra-pulmonary or cardiac disease.

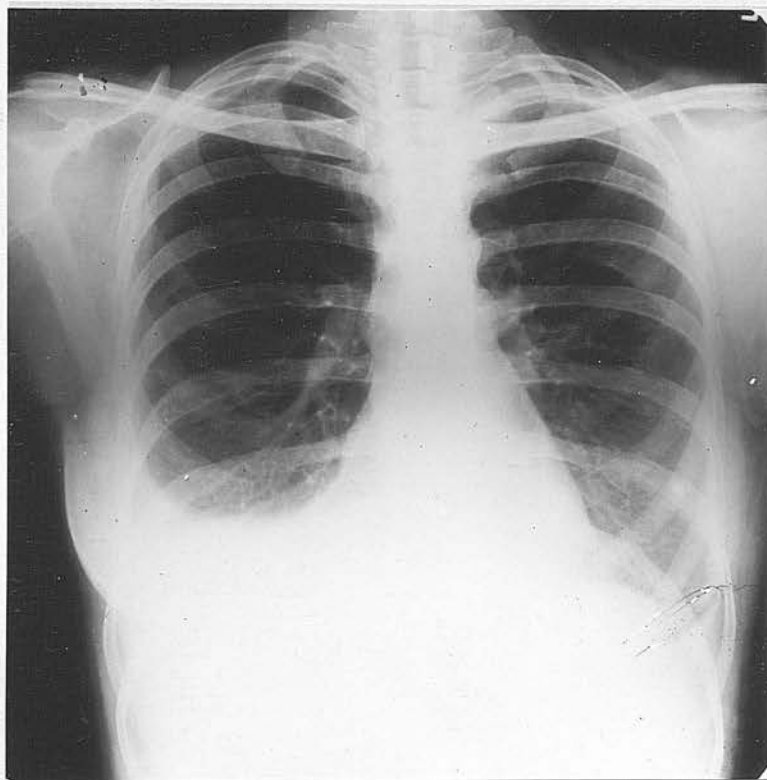


Fig. 69. Case 2.

Chest X-ray one year after the original left pleurisy and three months after exacerbation of rheumatoid arthritis associated with acute right pleurisy. A right pleural effusion is present. The left pleural effusion - see Fig. 68 - has largely absorbed. A feature of both effusions was their chronicity.

deviation; there was stony dullness at the right lung base indicating a pleural effusion. She was also found to have a mild diabetes mellitus which was subsequently controlled by dietetic restriction.

A chest X-ray soon after admission (Fig. 70) showed a right pleural effusion and a suggestion of left pleural effusion; the shape of the heart was mildly suggestive of a small pericardial effusion, but there was no clinical evidence of pericarditis. The possibility of the pleural effusions being cardiac transudates was considered, but right thoracentesis gave a clear serous fluid with high protein content - 4.5 Gms%, and a polymorph exudate; the fluid was sterile on culture. The onset of the illness with acute pleuritic pain was also more suggestive of an inflammatory lesion than a cardiac transudate.

The temperature chart of her first fortnight in hospital is reproduced (Fig. 71), and shows that there was no response to massive doses of penicillin. Later the pyrexia was controlled with disprin, and the right pleural effusion absorbed slowly. She was discharged on 29. 9.51 - i.e. after three months in hospital. At the time of her discharge, her general health was poor; the rheumatoid arthritis was still active, with E.S.R. 65 mm. in 1 hour.; there was slight residual dullness at the right lung base.

She was re-admitted on 5.10.51, with an attack of acute left pleurisy and fever; on this occasion no effusion developed, and the pyrexia subsided within a few days. The joint changes were still those of active rheumatoid arthritis. In view of the consecutive right and left pleuritis and the possibility of pericarditis in the original chest X-ray and the presence of arthritis, disseminated lupus erythematosus was considered as an alternative diagnosis, but no other evidence in support of this was forthcoming. The chest X-ray was repeated on 10.11.51 (Fig. 72). It showed the presence of an unusual consolidation near the hilum on the left side, with slight scattered opacities in the right upper lobe. Although the appearances were not specially suggestive of tuberculosis, a series of six gastric juices were examined both directly and by culture for tubercle bacilli, with negative results. Shortly after this the patient was discharged and has since been bed-ridden at home with advanced rheumatoid changes. It has not been possible to have another chest X-ray.

Comment. This case is more complicated than case 2.

Again there is little doubt about the diagnosis of rheumatoid arthritis, which was of such severity that

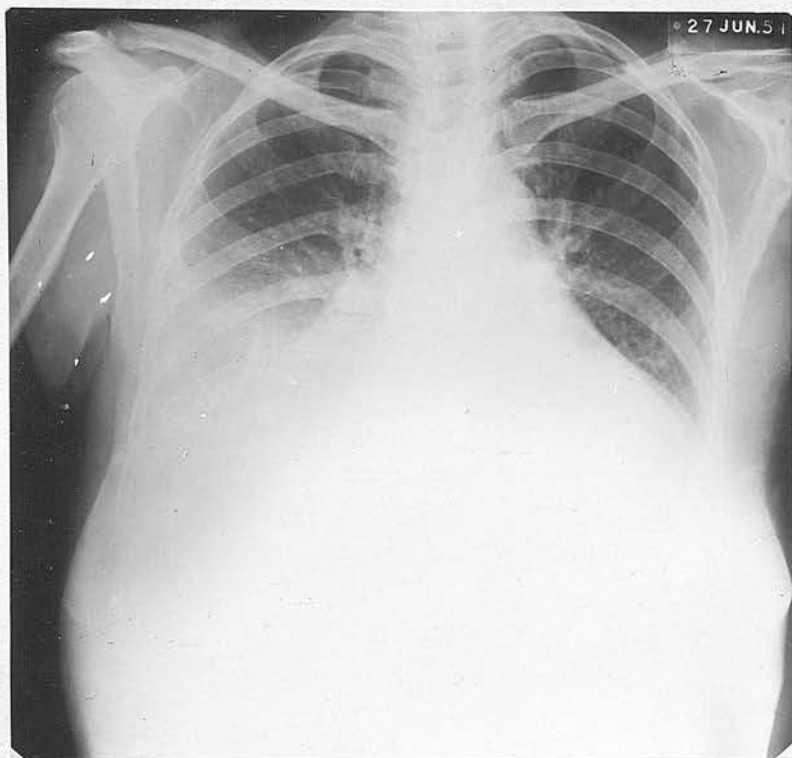


Fig. 70. Case 3.

Chest X-ray showing right pleural effusion, some enlargement of the cardiac shadow and obscuring of the left costo-phrenic angle. Those findings are discussed in the text.

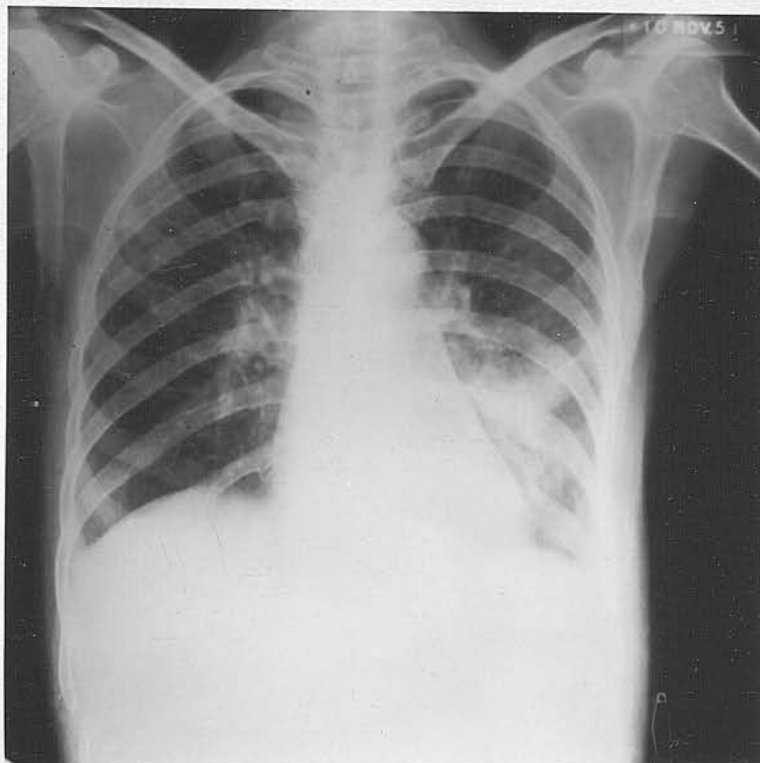


Fig. 72. Case 3.

Chest X-ray following re-admission to hospital with left febrile pleurisy. There is consolidation near the left hilum with scattered opacities in the right upper lobe.

"tuberculous rheumatism" can almost certainly be excluded. As in case 2, there was consecutive bilateral pleurisy. The weight of evidence is against the effusions being cardiac in origin, but in view of the first chest X-ray this possibility cannot be entirely excluded. At the time of the initial pleurisy there was no clinical or radiological evidence of underlying lung consolidation and there was no response of the pyrexia to penicillin (it later responded to disprin). On the other hand, the fluid had a polymorph exudate consistent with simple inflammatory origin. The later development of unusual pulmonary consolidation coinciding with the second pleurisy presented a difficult diagnostic problem. The changes were not typical of pulmonary tuberculosis and no tubercle bacilli could be recovered from the gastric juice. The consolidation did not resemble the "rheumatoid pneumonia" described by Ellman and Ball (1948), in which reticulation seems to be the main radiological feature. An ordinary unresolved pneumonia could certainly produce such changes. No final conclusion can be drawn. One would hesitate to ascribe all the pulmonary and pleural pathology to rheumatoid lesions.

Case 4. A female patient aged 53 was admitted to hospital on 13.12.47. 10 days prior to admission she had a mild sore throat with shivering and malaise. In the course of the next week, she developed pain and stiffness in both knees, both shoulders, both elbows, both wrists and the small joints of the hands. Her own doctor had prescribed salicylates without effect.

On examination, the affected joints were

swollen and tender, E.S.R. was 75 mm. in 1 hour and W.B.C. count 14,000 per cu.mm.. A chest X-ray (Fig. 73) showed loss of translucency at the left base suggesting a small pleural effusion. The diagnosis seemed to lie between rheumatic fever and acute rheumatoid arthritis. Accordingly, a further course of salicylate was given without effect on the symptoms or pyrexia - see temperature chart (Fig. 74).

In the third week of her illness, she developed an acute right pleurisy with rapid formation of an effusion. Right thoracentesis showed a clear serous effusion which was sterile on culture and contained numerous small lymphocytes and endothelial cells. The E.S.R. rose to 110 mm. in 1 hour. At this time there was a clinical impression that the size of the heart had increased slightly, probably indicating myocarditis, since there had been no evidence of pericarditis. In keeping with this, she had developed a mitral systolic murmur. It was felt, however, that the pleural effusion was definitely inflammatory in origin rather than a cardiac transudate because of the acute pleuritic pain and absence of any sign of cardiac failure.

In the course of the next two months, the whole illness gradually subsided with absorption of the pleural effusion and disappearance of the mitral systolic murmur. The joints returned to normal except for residual stiffness in the small joints of the hands. The E.S.R. also returned to normal.

She was seen again on 15.12.50, three years after the original illness. She still complained of stiffness in the finger joints, and examination showed slight spindling and limitation of movement. There was no muscular wasting and X-ray of hands was negative. Clinical and radiological examination of the heart showed no evidence of rheumatic disease. There was no radiological evidence of pulmonary tuberculosis.

Comment. Unlike cases 2 and 3, the diagnosis in this case was not conclusively established. The distribution of the joint involvement and the undoubted failure of response to adequate salicylates point to an acute rheumatoid arthritis. There was also no evidence of rheumatic heart disease on a three year follow-up. On the other hand, the course of the illness and the evidence of myocarditis could indicate an acute rheumatic fever. There was no

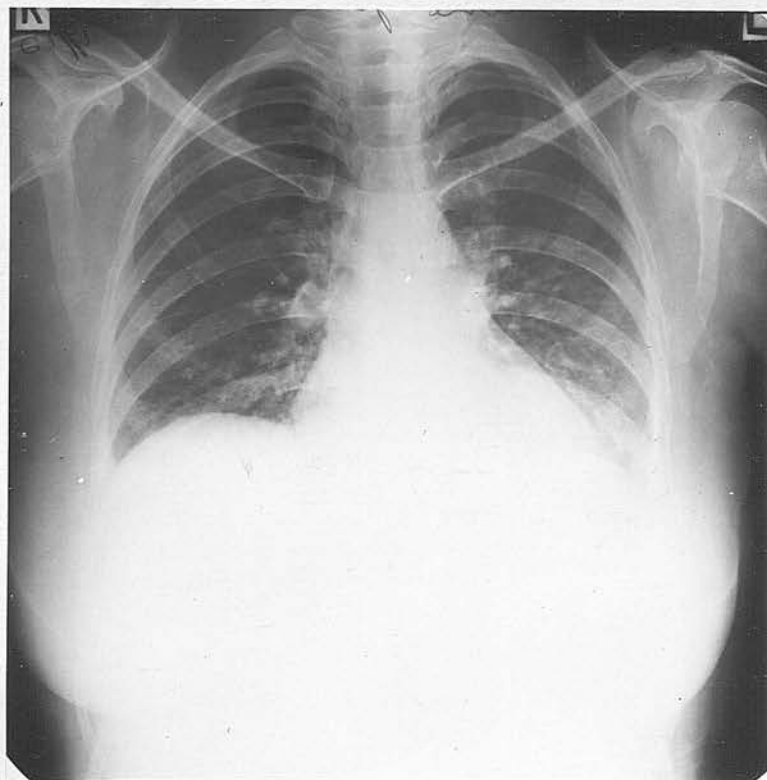


Fig. 73. Case 4.

Chest X-ray shortly after admission showing loss of translucency at left base suggesting a small pleural effusion. Later the patient developed an acute right pleurisy with effusion.

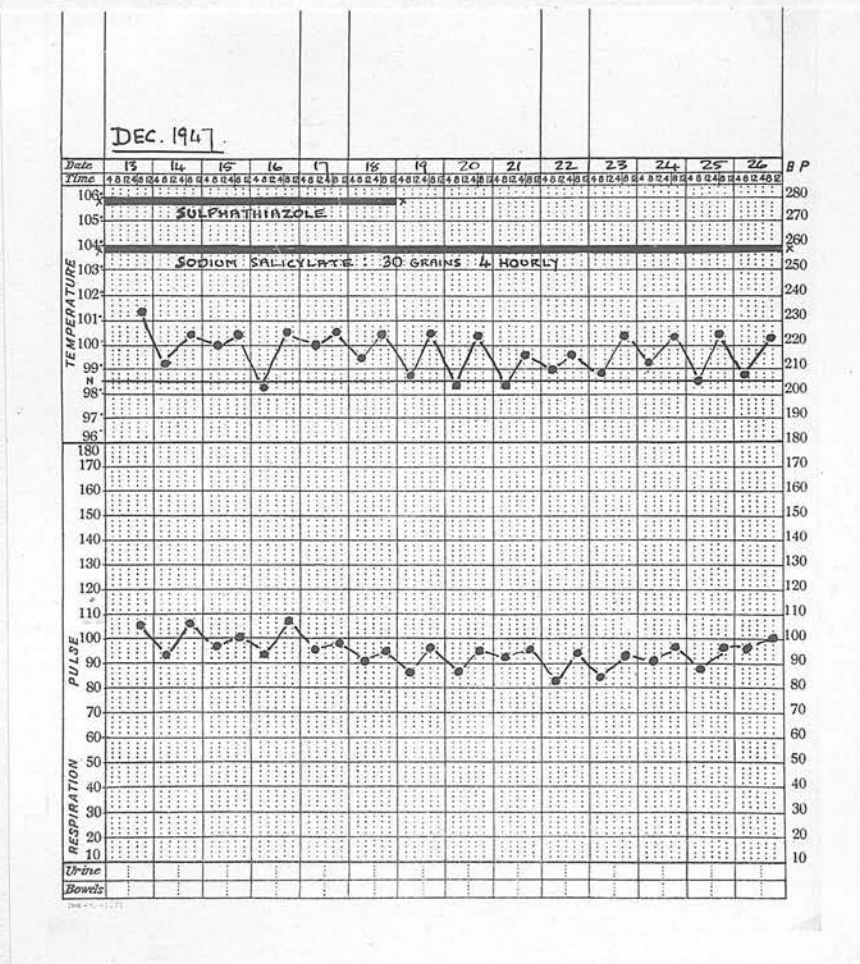


Fig. 74. Case 4.

Temperature chart of first fortnight in hospital. Joint symptoms and pyrexia failed to respond to salicylate therapy.

suggestion of disseminated lupus erythematosus. Tuberculous rheumatism again raises a problem, but the whole illness, with marked joint involvement and myocarditis, is more in favour of a "genuine" rheumatism. It seems reasonable to assume, in the absence of obvious pulmonary disease, that the bilateral pleural effusion was part of the rheumatoid (or rheumatic) process.

The three cases described above have been presented as examples of pleurisy and pleural effusion occurring during the course of rheumatoid arthritis. The weight of evidence suggests that the pleural involvement in cases 2 and 4 was actually part of the rheumatoid process; in case 3, the evidence is much more doubtful and constitutes a matter for discussion rather than a helpful contribution to the problem. If any one point is to be singled out for emphasis, it is that in all three cases the effusion was either simultaneously or consecutively bilateral, suggesting that a widespread pathological process was the cause; in keeping with this, it is known that rheumatoid arthritis is a widespread pathological process.

From the practical point of view, when dealing with pleurisy and pleural effusion complicating rheumatoid arthritis, the following points should be kept in mind.

1. Complicating or coincidental pulmonary disease may be the cause of pleurisy. Such disease includes

pulmonary tuberculosis, bronchopneumonia, bronchiectasis, pulmonary embolism and even bronchial carcinoma. Further, the effusion may be a transudate secondary to cardiac failure or amyloid disease. Reasonable steps, consistent with the fitness of the patient, should be taken to investigate those possibilities.

2. The phenomenon of tuberculous rheumatism requires serious consideration, although it is doubtful if in adults the joint involvement in this condition ever becomes as gross as in typical rheumatoid arthritis.

3. The onset of pleurisy in rheumatoid arthritis should always raise a suspicion that the whole condition is really disseminated lupus erythematosus, for which appropriate investigation and observation are required.

4. Pulmonary consolidation in rheumatoid arthritis may not be bacterial in origin. Rheumatoid pneumonia has been described - Ellman and Ball (1948), and there is no reason why it should not be associated with rheumatoid pleurisy. Rheumatoid pneumonia, however, should not be lightly diagnosed.

5. An occasional case of hypertrophic pulmonary osteoarthropathy, perhaps associated with bronchiectasis or bronchial carcinoma plus pleural effusion, may masquerade as a case of rheumatoid arthritis.

6. If the points above are given due consideration and nothing definite emerges, there is no harm in regarding the pleural involvement as part of the

rheumatoid process.

7. As Littler (1952) points out, the collagen diseases are all inter-related and it may be that rheumatoid arthritis with pulmonary and/or pleural involvement is a mild and non-progressive form of disseminated lupus erythematosus. This hypothesis provides a comfortable resting place for discussion on those problems.

Rheumatic Fever

There is a divergence of opinion among physicians about rheumatic pleurisy. In a Honyman Gillespie Lecture delivered in Edinburgh, Laurie (1950) stated, "In a dubious position is rheumatic pleurisy. There are some who doubt the existence of such a clinical entity. Others go so far as to account it second only to tuberculosis as a cause of sero-fibrinous exudations".

During the years 1946 to 1952, the author has had access to all cases of pleurisy, pleural effusion and rheumatic fever admitted to five medical charges in the Royal Infirmary of Edinburgh. During that period, only 3 cases were thought by the Physician-in-charge to present features in any way suggestive of the existence of rheumatic pleurisy.

Case 5. A male patient aged 13 presented with typical rheumatic fever. There was polyarthrititis, and pericarditis which went on to a small pericardial effusion. Later there was evidence of fluid in the left pleural cavity. Left thoracentesis gave a clear, serous fluid which was sterile on culture; protein content was 1.1 Gms. per 100 mils.; the

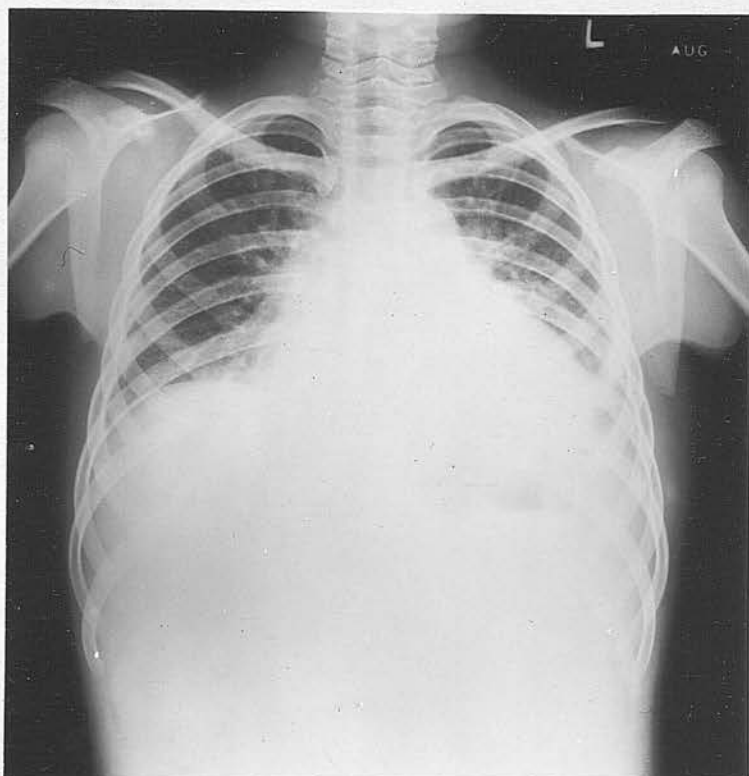


Fig. 75. Case 5.

Chest X-ray at time of left pleural effusion (transudate). There is a pericardial effusion with congestive changes in the lung fields.

cell content was an equal mixture of serosal cells and lymphocytes. Chest X-ray (Fig.75) showed a large heart shadow with congestive changes in the lung fields and a small left pleural effusion.

Comment. There was little reason to suspect rheumatic pleurisy in this case. Pleuritic pain was absent. The left pleural effusion was almost certainly a transudate secondary to cardiac embarrassment.

Case 6. A female patient aged 24 was admitted to hospital on 22.10.49. She had become ill a month previously with fever and vague pain in the front of the chest. There was a past history of repeated sore throats. On clinical examination, she had a widespread pericardial friction and collapse of the lower lobe of the left lung (Bamberger's Sign). Chest X-ray on 24.10.49 showed a slightly enlarged heart - ?pericardial effusion - and the collapsed left lower lobe. Despite the absence of joint pains, a provisional diagnosis of rheumatic pericarditis was made. A moderate pyrexia present on admission subsided rapidly coincident with salicylate therapy. Progress in the next few weeks was entirely satisfactory and she was discharged without symptoms or signs, and with a normal E.S.R., on 5. 1.50.

After discharge, however, she did not feel well, and in the next few months had several attacks of bilateral pleuritic pain. She was admitted again on 9. 6.50. Clinical examination of the heart revealed only a third heart sound in the mitral area, but there was a moderately large right pleural effusion. E.S.R. was 5 mm. in 1 hour. Chest X-ray showed a normal heart and confirmed the presence of a right pleural effusion. Right thoracentesis showed a clear, serous fluid with lymphocytic exudate; it was sterile on culture and failed to grow tubercle bacilli on Lowenstein-Jensen medium.

Tuberculosis was now strongly suspected and eventually confirmed by the growth of tubercle bacilli on Lowenstein-Jensen culture from 4 of 6 specimens of gastric juice. Even so, serial chest X-rays showed no tuberculous lesion of the lung parenchyma. In the course of the next year, the patient developed chronic constrictive pericarditis with massive recurrent ascites. At the time of writing she has just undergone a successful operation of pericardiectomy.

Comment. This case illustrates how easy it is to miss a diagnosis of tuberculous pericarditis; misleading features were the previous history of

repeated sore throats, the apparent response of pyrexia to salicylate therapy and the satisfactory clinical course to apparently complete cure. Not enough attention was paid to the absence of joint pains. The subsequent development of pleurisy with effusion might easily have been wrongly attributed to rheumatic pleurisy by an enthusiast for this diagnosis.

Case 7. A female patient aged 26 was admitted to hospital on 10. 3.50. She had been ill for some days with left pleuritic pain, fever, aching muscles and pain in the lumbar region. Shortly after admission, she developed a pericarditis which went on to effusion. The provisional diagnosis was rheumatic fever.

The pericarditis cleared up to be succeeded by recurrence of the left pleurisy which went on to effusion. W.B.C. count was 21,000 per cu.mm.. Left thoracentesis gave a clear, serous fluid which was sterile on culture and contained a polymorphous exudate. Although some thoughts of rheumatic pleurisy were entertained, tuberculosis now seemed a more likely diagnosis, especially since the pyrexia failed to respond to salicylate therapy. A somewhat belated X-ray of the lumbar spine revealed active spinal tuberculosis.

Comment. In this case, although no joint pains were present, the aching muscles suggested a rheumatic basis. A diagnosis of rheumatic pleurisy would have been a serious error. It is clear that both the pericarditis and pleurisy with effusion were due to haematogenous tuberculosis.

Discussion.

Of a large number of cases of pleurisy, pleural effusion and rheumatic fever observed in five medical charges of the Royal Infirmary of Edinburgh over a

period of approximately six years, only 3 cases gave rise to suspicion of the existence of rheumatic pleurisy. Those 3 cases have been described to illustrate how the suspicion arose and how, in each case, it proved to be unfounded. It is probably reasonable to conclude that rheumatic pleurisy, if it exists, is exceedingly rare.

Some authors who believe in the existence of rheumatic pleurisy emphasise that it is usually a dry pleurisy. Edström (1944) observed 1369 cases of rheumatic fever of which 4.5% were thought to have a dry pleurisy; none developed effusion. Robson (1944) and Giese (1944) state that the pleurisy is "usually dry" and constitutes an unimportant incident in the midst of the other features of a severe attack of rheumatic fever. On the other hand, Laurie (1950) states that a small effusion may form and is often haemorrhagic. Hangarter (1944) describes 5 cases of pleurisy with effusion thought to be rheumatic in origin; his criteria for differentiating the rheumatic from the tuberculous are unconvincing, viz.

- i. Tuberculous pleurisy is less rapid in onset, less painful and does not pursue such a stormy course.
- ii. Tuberculous fluid remains for a long time.
- iii. Rheumatic pleurisy is frequently preceded by exposure to cold or a change in climatic conditions.
- iv. In rheumatic pleurisy the E.S.R. is higher - 60 - 100 mm. in 1 hour.

v. Rheumatic pleurisy may be associated with erythema nodosum.

With regard to v., it is probable that most clinicians regard the association of pleurisy and erythema nodosum as almost certainly indicating a tuberculous aetiology.

Lees (1952) refers to the difficulty in estimating the part played by cardiac insufficiency in the production of pulmonary and pleural pathology in rheumatic fever - see also Case 5. He then describes 2 cases of polyarthrititis with pulmonary consolidation and pleural effusion; in both it is reasonably certain that cardiac insufficiency was not a factor.

No satisfactory conclusion on the problem of rheumatic pleurisy is possible. The weight of evidence suggests that if the pleurisy is "dry" and occurs in the midst of the other typical features of rheumatic fever, there is no harm in making a diagnosis of rheumatic pleurisy. If the pleurisy is "wet", tuberculosis should not be lightly excluded even when other clinical features are suggestive of a rheumatic illness - joint pains and pericarditis may also occur in tuberculosis; further, pleural fluid may be the result of cardiac insufficiency due to severe rheumatic carditis.

Scleroderma

There is no specific reference in the literature

to pleural lesions in scleroderma, although it is now widely known that, in occasional cases, typical pulmonary changes in the nature of a cystic pulmonary sclerosis occur - Murphy, Krainin and Gerson (1941); Getzowa (1945). Myocardial fibrosis with cardiac failure has also been reported - Weiss, Stead, Warren and Bailey (1943). It is clear, therefore, that pleural pathology may be either secondary to cardiac failure or secondary to infection occurring in a cystic lung.

Case 8. A female patient aged 48 was admitted to hospital on 3. 9.46. On examination, she was a frail ill-looking woman. The skin of the face and hands showed marked sclerodermatous changes. X-ray of hands showed calcinosis in the soft tissues of the right thumb with bone atrophy in the terminal phalanges of the thumbs and fingers. X-ray of chest (Fig. 76) showed the typical cystic pulmonary sclerosis of scleroderma, and some cardiac enlargement.

Progress was steadily downhill. Following an attack of paroxysmal tachycardia confirmed by E.C.G., she developed signs of fluid at both lung bases. Thoracentesis was not performed. She died on 30.12.46.

Necropsy summary was -

i. Cardiac failure with chronic venous congestion of liver, and pleural, pericardial and peritoneal effusions.

ii. Sclerodermatous changes in skin with subcutaneous calcinosis.

iii. Myocardial fibrosis.

iv. Cystic disease of lungs with necrotising pulmonary arteritis and endarteritis obliterans.

v. Fibrous pleural adhesions and non-specific pleural fibrosis.

Comment. The pleural effusions detected clinically at both lung bases and demonstrated at autopsy were transudates secondary to scleroderma heart disease.

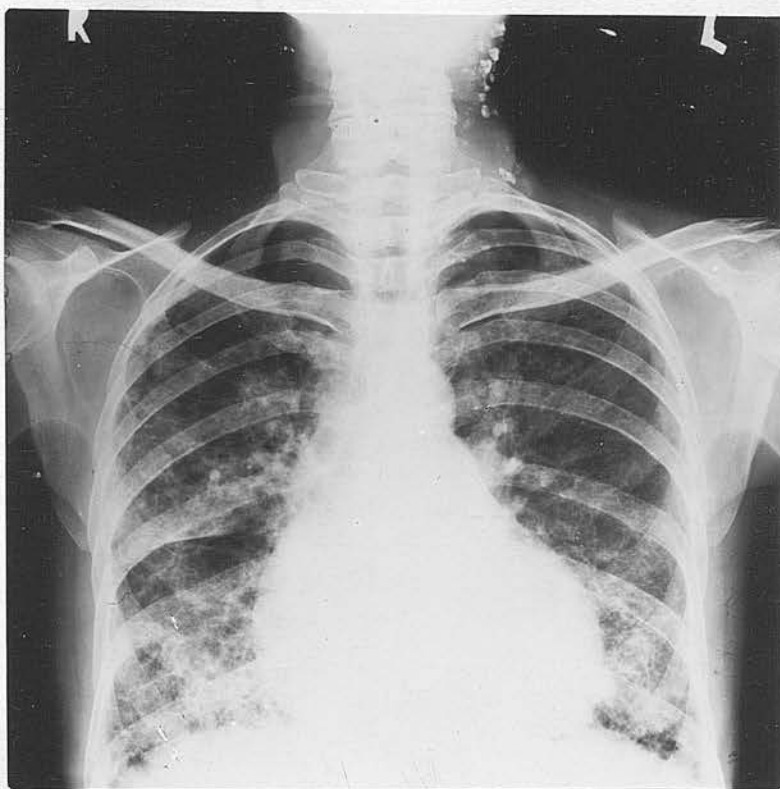


Fig. 76. Case 8.

Chest X-ray showing typical cystic pulmonary sclerosis of scleroderma and cardiac enlargement due to scleroderma heart disease. The patient later developed a bilateral pleural transudate.

There was no evidence of pleural pathology specific to scleroderma. There was no secondary infection in the cystic lung spaces.

Case 9. A male patient aged 57 was admitted to hospital on 13.12.48. For the past three months he had complained of attacks of "Raynaud's Phenomenon", affecting both hands; on exposure to cold, the fingers would become cold and white and later turn blue; following an attack, the fingers were swollen and painful for some hours. The feet also tended to become cold and painful in cold weather. In addition, he had experienced several mild attacks of left pleuritic pain during the past two months. Otherwise he had no respiratory or cardiac symptoms.

Prior to his admission to the medical ward, he had been completely investigated at the Peripheral Vascular Unit by Professor Sir James Learmonth, who stated that "the poverty of the peripheral circulation was secondary to a more wide-spread disturbance and that sympathectomy was not indicated."

On clinical examination, he had early sclerodermatous changes in the fingers with excessive "firmness" of the skin and mild flexion deformity, particularly of the distal interphalangeal joints. There was some atrophy of the dorsal interossei causing a superficial resemblance to rheumatoid arthritis, but X-ray of hands and wrists was negative. He was examined by a Neurologist who could find no evidence of neurological disease. There was no alteration in the facial skin. The feet were cold, but otherwise normal. Examination of the chest showed dullness at both lung bases with creaking pleural friction on the right side. X-ray of chest (Fig.77) showed small effusions at both lung bases, and possible chronic inflammatory changes in both lower lobes; there was no evidence of cystic pulmonary sclerosis. The cardiovascular system was normal. There was no pyrexia or tachycardia. E.S.R. was 40 mm. in 1 hour. Bilateral thoracentesis revealed clear, serous fluid on both sides; both fluids were sterile on culture and contained lymphocytes. Sputum was consistently negative for tubercle bacilli.

Treatment was instituted with wax baths to the hands. No improvement took place and he was discharged on 24.1.49. At the time of his discharge, he still had dullness at both lung bases and friction on the right side. The patient went to live in Wales and could not be traced for follow-up purposes.

Comment. There is little doubt that this patient was suffering from early scleroderma, having presented, as scleroderma commonly does, with Raynaud's

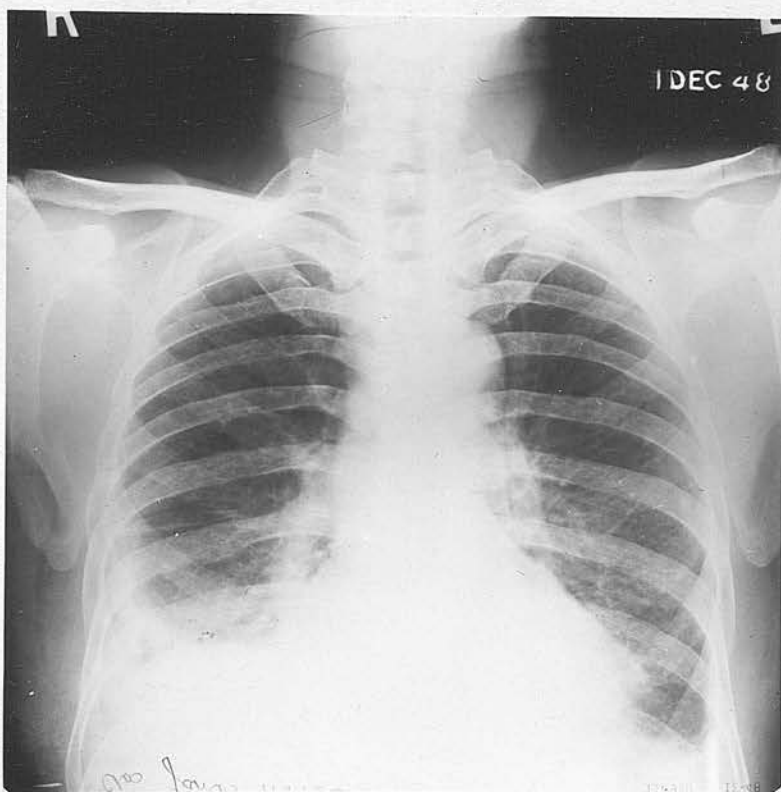


Fig. 77. Case 9.

Chest X-ray showing small effusions in both pleural cavities with inflammatory changes in both lower lobes - especially the right. There is no definite evidence of cystic pulmonary sclerosis.

Phenomenon. There was no radiological evidence of cystic pulmonary sclerosis and no reason to suspect cardiac failure. Even so, he had chronic bilateral pleural effusion with long continued coarse pleural friction on the right side. Despite the absence of pyrexia and the absence of chest symptoms other than pleuritic pain, it is probable, from the radiological evidence, that the pleural effusions were secondary to chronic inflammatory changes in the lower lobes of both lungs. Unfortunately, bronchography was not done. Tuberculosis was excluded with reasonable certainty. It is possible that the chronic inflammatory changes in the lungs were in part secondary to commencing sclerodermatous lesions. Finally, it would be unwise to postulate a specific sclerodermatous pleurisy in this case.

Case 10. A female patient aged 45 was admitted to hospital on 8.1.52. Her complaints were

- i. Raynaud's Phenomenon affecting the hands and feet for 5 months.
- ii. Swelling of the face, arms and legs for 4 months.
- iii. Excessive fatigue for 4 months.

On examination, there was pitting oedema of the face, arms and legs. It was soon obvious that this was not due to any ordinary cause - urine was consistently free from albumin, plasma proteins were normal, there was no evidence of "allergy" and cardiovascular system was normal. X-ray of chest (Fig. 78) showed increased markings in both lung fields and hazing of both costo-phrenic angles; it was thought at the time that those changes might indicate pulmonary oedema with small pleural effusions. Diagnostic thoracentesis was not done. A complete E.C.G. study was normal.

After admission to hospital, she was found to have an irregular pyrexia and tachycardia (Fig. 79). Thorough investigation, appropriate to a case of



Fig. 78. Case 10.

Chest X-ray shortly after admission to hospital showing increased markings in both lung fields and hazing of both costo-phrenic angles. It is probable that those changes represented pulmonary oedema with small pleural effusions.

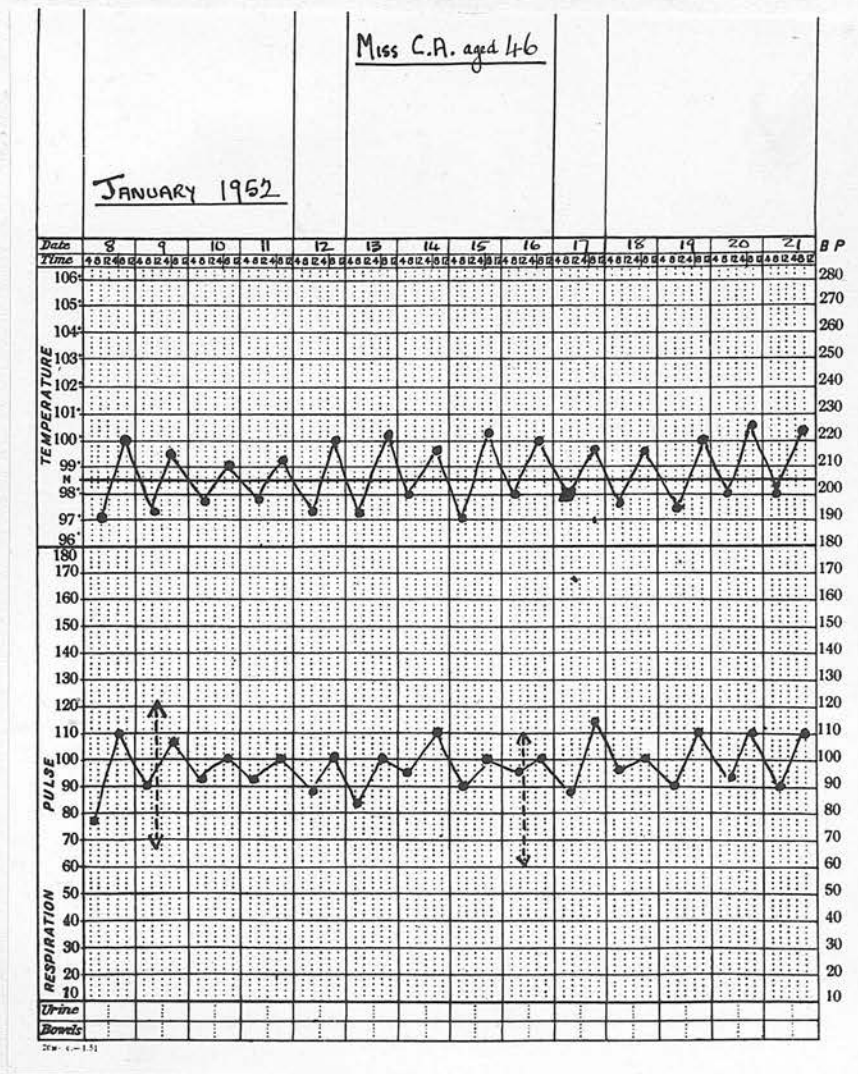


Fig. 79. Case 10.

Temperature chart of first fortnight in hospital showing irregular pyrexia and tachycardia.

"P.U.O.", was completely negative. Sputum was consistently negative for tubercle bacilli. The white blood cell count remained normal. X-rays of hands and feet showed no abnormality.

After some weeks of rest in bed without other specific therapy, the pyrexia and oedema became less. Examination of the skin of the face and hands now revealed changes, previously obscured by the oedema, typical of scleroderma. She was eventually discharged, in reasonable health, on 13. 3.52. Progress at home was unsatisfactory. Subcutaneous oedema and pyrexia returned. She was re-admitted on 7. 6.52. At this time, her clinical state was much the same as at her first admission except that the sclerodermatous changes were more marked. There was dullness at both lung bases consistent with the presence of small pleural effusions. The pyrexia was of the same type and degree as before.

In view of the obviously grave prognosis, she was given a course of A.C.T.H.. As expected, no improvement occurred. Her blood pressure, previously 120/70, rose to 190/90. Because of this, the A.C.T.H. was stopped. Death occurred suddenly on 27. 7.52, 10 days after the cessation of A.C.T.H..

Necropsy showed the following -

A. Macroscopic. Apart from subcutaneous oedema and approximately 600 c.c. of fluid in each pleural sac, no significant abnormality was detected.

B. Microscopic. The report is given in detail.

Heart : N.A.D.

Lungs : In addition to oedema, there is a minor degree of eccentric intimal fibrosis of many small arteries. Elastic tissue is sometimes thinned out in such places but has not been destroyed. Here and there in the pleura, collagen fibres are swollen and fused together into hyaline masses to which there is no significant inflammatory response (Fig. 80).

Submandibular Gland : The amount of lymphoid tissue is somewhat in excess of normal but no abnormality is seen in the parenchyma, interstitial tissue or vessels.

Liver : There is a good deal of congestion which is of generalised rather than the more usual centrilobular distribution. Toxic changes in the parenchyma are the only other abnormality.

Brain : (cerebrum) N.A.D.

Kidneys : The lesions here are striking and diagnostic. Many interlobular arteries are greatly narrowed by marked concentric intimal thickening in

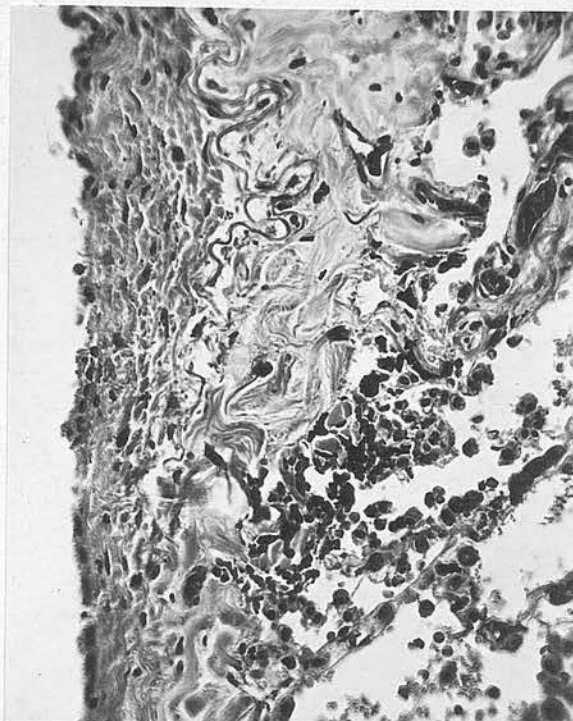


Fig. 80. Case 10.

Section of Pleura. H. and E. x 250.

In the upper part of the section, collagen fibres are swollen and fused together into hyaline masses to which there is no significant inflammatory response. This appearance indicates a specific sclerodermatous lesion of the pleura.

the form of oedematous fibrous tissue containing moderate numbers of proliferating fibroblasts or irregular shape. Intact endothelium is often seen on the inner aspect of this fibrous tissue and thrombosis is absent. The internal elastic lamina is usually readily seen stretched out and intact around the intimal proliferation and the media is also intact around this.

Superimposed on this lesion there is segmental fibrinoid necrosis of media or intima without any inflammatory response or haemorrhage. The necrotic lesion is also seen in afferent arterioles unaffected by the proliferative lesions and spreads from the arterioles into parts of related glomeruli. Other glomeruli show ischaemic fibrosis and yet others are merely deeply congested.

The vascular lesions have resulted in atrophy and degeneration - sometimes amounting to early necrosis - of convoluted tubules. There is little or no inflammatory response.

Adrenals : Collagen fibres in parts of the capsule are swollen, hyaline and fragmented. No inflammatory response is seen. In some small vessels in the zona glomerulosa patches of fibrinoid change are present in intima or media. The intense cellular intimal reaction seen in the kidneys is absent, but on the other hand there is no elastosis or hyaline change, such as accompanies hypertension.

Skeletal Muscle: (two blocks). In one block, the main feature is the presence of many lymphorrhages of varying size, the largest being about 1 mm. in diameter. Along one side of the section collagen fibres are markedly swollen, have lost definition and show patchy fibrinoid change. This is accompanied by a relatively mild lymphocyte-histiocyte infiltration. In the other section large clumps of hyaline fibrous tissue are seen in which individual fibres are swollen and ill-defined. Muscle fibres show mild degenerative changes.

Skin : Blocks were taken from forehead, lip and thigh. The appearances vary in these different situations, but one feature is common to them all - swelling and loss of definition of collagen fibres in skin and subcutaneous tissue. In the forehead and to a lesser extent in the lip, the swollen fibres have fused superficially to form dense hyaline masses just under the epidermis and sometimes in underlying muscle. In the thigh, individual fibres are greatly swollen but have not fused. Oedema is also present in all sections being most marked in the superficial dermis of the thigh. The epidermis shows atrophy, particularly in the thigh, where rete pegs and dermal papillae are almost non-existent. Dermal appendages

are also atrophic, particularly sweat glands. Inflammatory changes are minimal and take the form of very occasional perivascular collections of lymphocytes. In the section of lip some small arteries show the cellular intimal fibrosis described in the kidneys, though to a much less marked extent.

Interphalangeal Joint: N.A.D.

Comment by Pathologist: This is a most interesting case, which corresponds closely from the pathological point of view with those reported by Moore and Sheehan (1952). The skin lesions are undoubtedly those of scleroderma and there is evidence of the same type of lesion in collagen in the pleura, skeletal muscles and adrenal capsules. The vascular lesions in the kidneys are apparently peculiar to this disease and are readily distinguishable from those of essential hypertension or polyarteritis nodosa.

The changes in one block of skeletal muscle are very like those of systemic lupus erythematosus, but this condition is ruled out by the absence of typical renal and splenic lesions. The pleural effusions would also appear to be part of the disease.

Comment. This undoubted case of scleroderma presented with the usual feature of Raynaud's Phenomenon and the highly unusual features of pyrexia and generalised oedema - including pulmonary oedema and bilateral pleural effusion. Unfortunately, thoracentesis was not done during life, but the effusions were confirmed at necropsy. There was no clinical reason to suspect a cardiac cause for the oedema; at necropsy, there was no evidence of cardiac failure and the heart was normal. At no time was there albuminuria or hypoproteinaemia. It is therefore reasonable to conclude that the oedema of the skin, lungs and pleural cavities was part of the sclerodermatous process shown to be present in those structures. Apart from the unusual renal lesion,

which is not relevant to the present discussion, the specific sclerodermatous lesion of the pleura is of great interest.

It is improbable that the A.C.T.H. therapy was the cause of any of the necropsy findings. The oedema of the skin, lungs and pleural cavities was present many months before A.C.T.H. was given. No evidence of A.C.T.H. toxicity was present apart from the hypertension. Indeed, it is probable that the hypertension was due to the renal lesion rather than the A.C.T.H., since the pressure remained elevated for 10 days after cessation of A.C.T.H..

This case would seem to illustrate a particularly acute form of scleroderma producing pyrexia and widespread oedema as integral parts of the pathological process. Perhaps this form of scleroderma is closely allied to another collagen disease, namely acute disseminated lupus erythematosus. It would not be true to say that sclerodermatous pleurisy occurred in this case. There was no history of pleuritic pain. The pleural effusions were more in the nature of "pleural oedema". Certainly they were not in the nature of cardiac transudates; nor could they be secondary to inflammatory changes in cystic lung spaces, since there was no evidence of such cystic change at necropsy.

Periarteritis Nodosa

Periarteritis nodosa (polyarteritis nodosa) is a widespread disease of arteries leading to protean clinical manifestations. The lungs and pleura may certainly be involved, but a study of the literature suggests that systems other than the respiratory bear the main impact of the disease. In 3 cases observed by the author, there was no clinical or radiological evidence of pulmonary or pleural lesions.

Rose, Littmann and Houghton (1950) state that the common respiratory symptoms are cough, pain in the chest and asthmatic attacks. Dyspnoea, when present, is usually secondary to the asthma or to cardiac failure. Miller and Daley (1946) state that chest pain is a rarity and is usually due to pleurisy secondary to pulmonary infarction, although pericarditis and involvement of the intercostal nerves may be occasional causes. The typical radiological appearance of pulmonary involvement is a fan-like infiltration extending outwards from both hilar regions - Herrman (1933), Wiener (1933), Weir (1939). Terminal miliary abscesses - Sandler (1938), and transient infiltrations in the lower lobes - Elkeles and Glynn (1944) have also been described. Typical pathological changes in the pulmonary arteries have been described by Ophüls (1923). There is no reference in the literature to specific pleural pathology, although Hermann (1933) and Rose et al (1950)

indicate that bilateral pleural effusion may occur secondary to pulmonary infarction.

It would seem that pleural lesions in periarteritis nodosa are of little practical clinical importance, occurring, as they do, somewhat infrequently in the midst of numerous other more important symptoms and signs. Such lesions are likely to be secondary to pulmonary infarction.

SECTION VIIPLEURAL EFFUSION IN RETICULOSIS

In the first place it should be emphasised that with the notable exception of acute leukaemia, which may begin as an acute pleurisy with effusion, pleural fluid due to a reticulosis is unlikely to present an aetiological problem since, for practical purposes, it is a complication occurring, as a rule, late in the course of a previously diagnosed and clinically obvious case. Even so, it is interesting to note the type of reticulosis which is likely to give rise to pleural effusion, and to illustrate this, one cannot do better than reproduce the following table from a post-graduate lecture delivered in Edinburgh by Dr. Margaret Tod of Manchester - Tod (1952).

TABLE 26

Complications - Hodgkin's and Brill-Symmer's Disease

<u>Path. Report</u>	<u>No.</u>	<u>Fever</u>	<u>Anaemia</u>	<u>Serous Effusion</u>
Hodgkin's Disease	275	32%	35%	8%
Brill-Symmer's Disease	24	0%	25%	33%

Apart from the differences indicated in Table 26, there is a close clinical resemblance between Hodgkin's Disease and Brill-Symmer's Disease. Pathologically, however, they are quite different, lymph gland biopsy in the latter showing well-defined lymphoid follicle hyperplasia - hence the alternative name, lymphoid follicular reticulosis. It

is of interest that in the original description of the disease in 1925 by Brill, Baehr and Rosenthal, the frequency of serous effusion received comment; this is also mentioned by Hadfield and Garrod (1947).

As Tod's figures, obtained at a Department of Radiotherapy, indicate, Brill-Symer's Disease is relatively uncommon. The author has observed personally only two cases, both of which were complicated by pleural effusion.

Case 1. A female patient aged 63 was admitted to hospital with generalised lymphadenopathy, splenomegaly, ascites and bilateral pleural effusion. Lymph gland biopsy was typical of Brill-Symer's Disease. Pleural fluid was aspirated from the left pleural cavity; it was slightly hazy and clotted on standing; protein content was 3.75 Gms. per 100 mls.; no growth was obtained on culture; thorough cytological investigation showed a non-specific picture: lymphocytes 76%, serosal cells 23%, polymorphs 1%. Radiotherapy led to considerable clinical improvement.

Comment. The character of the fluid suggested an exudate, which in turn suggested direct invasion of the pleura by the pathological process rather than transudation due to lymphatic and/or venous obstruction. It is not surprising that the cytological picture was non-specific, since the essential pathology is simply hyperplasia of lymphocytes.

Case 2. Brief reference has already been made to this patient in Section IV, page 129. A male aged 48 was admitted to hospital on 28.10.47. He had taken ill one week previously with an acute febrile pleurisy on the right side. Clinical examination revealed a large right pleural effusion and very small shotty glands in the neck, axillae and groins. X-ray of chest showed only the pleural effusion, there being no evidence of mediastinal lymphadenopathy. Examination of the peripheral blood showed no abnormality. The pleural fluid was clear and

serous, sterile on culture and with protein content 4.1 Gms. per 100 mls.; the cytology was lymphocytes 80%, serosal cells 20%.

The pyrexia subsided after 4 days. A chest X-ray on 17.11.47 - i.e. after 3 weeks - showed almost complete disappearance of the pleural fluid.. The lymph glands remained unchanged. He was discharged in excellent health on 27.11.47.

During the summer of 1948, he developed signs of superior vena caval obstruction. X-ray of chest on 5.10.48 showed mediastinal lymphadenopathy with recurrence of right pleural effusion. Biopsy of a neck gland showed the picture of Brill-Symmer's Disease. The patient died, after several courses of radiotherapy, in 1950. Necropsy was not possible.

Comment. The original illness seemed typical of a primary tuberculous pleural effusion, and insufficient attention was paid to the slight but definite lymphadenopathy. As in case 1, the fluid was an exudate, and the cytology was non-specific. It is of course possible that the pleurisy was not connected with the reticulosis, but it seems reasonable to associate them. If the association is accepted, this case is unusual in that pleural effusion was the presenting manifestation of a reticulosis.

Hodgkin's Disease.

Of 16 cases of Hodgkin's Disease observed by the author, only 1 developed pleural fluid which was bilateral and occurred late in the course of the illness. The cytology of the fluid proved of unusual interest in that it was diagnostic of Hodgkin's Disease - see pages 93 and 94.

Lymphosarcoma.

It is at present customary to regard lymphosarcoma, of both round-cell and reticulum-cell types,

as a form of malignant reticulosis. Again according to Tod (1952), it is distinctly unusual for pleural effusion to occur during the course of lymphosarcoma - only 2% of 321 cases. Presumably mediastinal lymphosarcoma is more liable to cause pleural effusion than lymphosarcoma at sites more distant from the pleura, although in such cases it is often difficult, short of necropsy, to exclude anaplastic bronchial carcinoma with secondaries in the mediastinal glands.

In view of Tod's figures, the following two cases are of some interest.

Case 3. A female aged 41 was admitted to hospital on 9. 7.49. For 8 weeks she had felt "off-colour" with loss of appetite and spasmodic shivering attacks. Recently she had felt breathless. There was no pain.

On examination, she was emaciated with a muddy complexion; there was a small left pleural effusion. W.B.C. count was 8,000 per cu.mm.. Chest X-ray on admission showed the effusion with normal lung fields and no evidence of mediastinal lymphadenopathy. Left thoracentesis gave a clear serous fluid which was sterile on culture and contained mainly lymphocytes; protein content was 3.64 Gms. per 100 mls..

Slight pyrexia subsided soon after admission, but her clinical state did not improve. E.S.R. remained elevated at 25 mms. in 1 hour. After 2 weeks, a bed became available at a Convalescent Home to which she was transferred as a possible case of primary tuberculous pleural effusion. Her progress there was also unsatisfactory. The appetite remained poor and she failed to gain weight. On 24. 9.49, she complained of upper abdominal discomfort. Clinical examination revealed a mass in the left hypochondrium which had not previously been detected. She was re-admitted to hospital on 26. 9.49.

The left pleural effusion was now larger. X-ray of chest (Fig. 81) showed the development of fine infiltrative shadows in the lower two-thirds of the right lung. Left thoracentesis gave a fluid in all respects similar to that of the previous thoracentesis. Since the mass in the left hypochondrium was thought to be spleen, a reticulosis was considered in diagnosis. Examination of the peripheral blood showed - Hb. 92%; W.B.C. 33,000 per cu.mm.

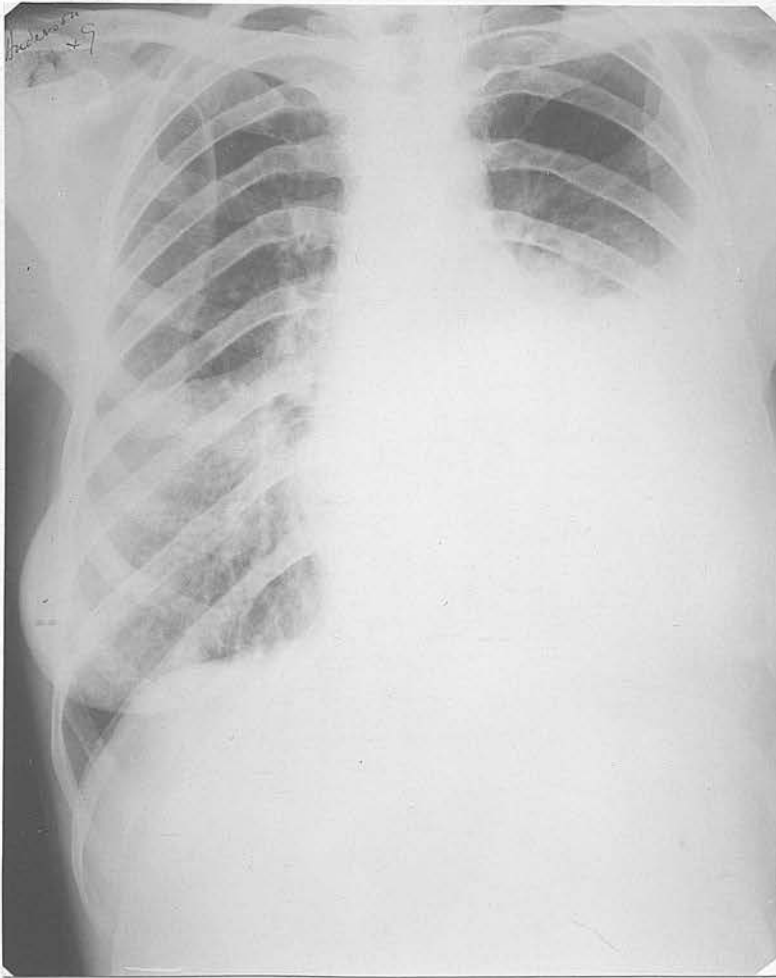


Fig. 81. Case 3.

Chest X-ray showing left pleural effusion secondary to lymphosarcoma of stomach. The infiltrative shadows in the right lung were proved at necropsy to represent small lymphosarcomatous deposits.

with polymorphs 18%, lymphocytes 80% and monocytes 2%. Sternal marrow was normal.

Progress was rapidly downhill and she died on 15.10.49. Necropsy showed

- i. Round-cell lymphosarcoma of stomach.
- ii. Multiple small deposits of lymphosarcoma in lungs.

Comment. In this patient, pleural effusion was the presenting manifestation of lymphosarcoma of the stomach. As might be expected, the pleural fluid showed a non-specific lymphocytic exudate. The original clinical picture was not quite typical of a primary tuberculous effusion - absence of pleuritic pain; exceedingly poor general condition not improving with rest in bed. Ultimately the primary tumour of the stomach was palpable, but was thought to be spleen. The lymphocytosis in the peripheral blood prior to death is an occasional finding in lymphosarcoma. The infiltrative shadows in the lungs seen in the last chest X-ray were due to lymphosarcomatous deposits.

Case 4. A male patient aged 48 was admitted to hospital on 5.11.48 for investigation of bilateral pleural effusion which had presented with steadily increasing dyspnoea without pleuritic pain. His previous medical history was interesting. In 1943 a laparotomy was performed because of a "swollen abdomen"; apparently a mass of glands was found and the patient was told that biopsy showed an atypical form of Hodgkin's Disease. He was given a course of radiotherapy. The abdominal swelling disappeared. Thereafter he had kept well until the onset of dyspnoea.

Clinical examination confirmed the presence of bilateral pleural effusion. Enlarged lymph glands were palpable in the left iliac fossa just above the inguinal ligament. There was slight hepatomegaly, but no splenomegaly or ascites. Blood examination

showed Hb. 96%.; W.B.C. 9,600 per cu.mm. with normal differential count. Chest X-ray showed the pleural effusions; there was no mediastinal or hilar lymphadenopathy. Samples of fluid from each pleural cavity were essentially the same in character, viz. clear and serous; no clot on standing; protein content 2.4 Gms. per 100 mls.; cells - lymphocytes 75%, polymorphs 5%, serosal cells 20%.

Initial management was difficult because of marked dyspnoea. Despite repeated aspirations of large quantities of fluid from each pleural cavity, there was no appreciable lessening of the effusions. A course of radiotherapy directed at the mediastinum was also ineffective - the expected result in the absence of mediastinal gland involvement. In the meantime, in view of the possibility of confusion between tuberculosis and Hodgkin's Disease in the original biopsy, an exhaustive examination for tubercle bacilli was carried out on the pleural fluid and gastric juice. This was negative. The clinical picture was in any case not typical of tuberculosis.

On 5.12.48 it occurred to the Physician-in-charge to estimate the plasma proteins, although no subcutaneous oedema was present. The result was Albumin 2.29 Gms. per 100 mls., Globulin 2.25 Gms. per 100 mls.. Treatment with a high protein diet was instituted with remarkable effect. The pleural effusions required no further aspirations, and indeed they cleared completely in the next two months. On 9. 2.49, the plasma albumin was recorded as 4.93 Gms. per 100 mls..

Thereafter the patient kept well until 1952 when there was a recurrence of bilateral pleural effusion. There was now radiological evidence of mediastinal lymphadenopathy. Radiotherapy had little effect. At necropsy, the thoracic and abdominal glands were infiltrated with reticulum-cell sarcoma; the pleura was normal.

Comment. This patient proved to have a reticulum-cell sarcoma of unusually long duration involving the abdominal and thoracic glands. At one stage, he developed pleural transudates which persisted until a low plasma albumin was corrected by a high protein diet. In the absence of oedema elsewhere, it would not be reasonable to attribute the transudates entirely to hypoproteinaemia, but there can

be little doubt that this was an important factor. There was no reason to suspect a cardiac factor, and, at the time, there was no evidence of mediastinal lymphadenopathy and no apparent response to radiotherapy. In the absence of other causes, the hypoproteinaemia was attributed to the reticulosis and perhaps to some restriction of food-intake due to anorexia.

Practical Applications.

1. Pleural effusion is rare in lymphosarcoma and Hodgkin's Disease, but is not uncommon in Brill-Symmer's Disease (lymphoid follicular reticulosis). The presence of pleural effusion in a patient with the features of a reticulosis is therefore of some slight help in diagnosing the type of reticulosis.
2. Pleural effusion is unlikely to be the presenting manifestation of reticulosis, but case 2 - Brill-Symmer's Disease - and case 3 - lymphosarcoma of stomach - show that this possibility exists and that tuberculosis may be wrongly diagnosed initially. In both those cases, however, there were features - e.g. slight lymphadenopathy, poor general health failing to respond to rest in bed - which were unusual for tuberculosis and which merited a review of the diagnosis.
3. In Brill-Symmer's Disease and lymphosarcoma, the "lymphocytic" nature of the pathology causes, in the pleural fluid, a non-specific lymphocytic cytological

picture, which is of no value in diagnosis. In Hodgkin's Disease, on the other hand, the cytological picture may be diagnostic - see pages 93 and 94 - or the presence of pleural eosinophilia may be suggestive - see page 33.

4. In case 4 - reticulum-cell sarcoma - hypoprotein-aemia was probably a factor in the production of bilateral pleural transudate. This point is possibly worth remembering in the event of effusions failing to resolve with radiotherapy.

SECTION VIIISTERILE, SEROUS PLEURAL EFFUSION OF
SIMPLE INFLAMMATORY ORIGIN

The problem of the sterile, serous pleural effusion complicating lobar pneumonia or more rarely, other types of pneumonia, is a relatively new one, since in the pre-chemotherapeutic and pre-antibiotic eras, frank empyema was the usual sequel to severe involvement of the pleura. It is said - Nairn (1949) - that 10% of all cases of lobar pneumonia develop a serous effusion. Crofton et al. (1951) studied 110 cases of pneumonia in West London; of the 110, 62 were classified as "lobar pneumonia"; of the 62, 10 developed a pleural effusion large enough to be aspirated which in 2 cases became an empyema; it is of interest that no case of pleural effusion occurred in the 48 pneumonias other than lobar.

Although those figures are quoted by Nairn and Crofton et al., it is difficult in both general and hospital practice to estimate the true frequency of this type of serous pleural effusion. Commonly the effusion is small and therefore difficult to detect on clinical examination. On other occasions, although the clinical signs may be suggestive of a layer of fluid overlying the consolidation, it is impossible to be certain of the presence of fluid without X-ray examination, or better, diagnostic puncture of the chest. In the author's experience,

most physicians, probably rightly, are averse to disturbing the pneumonia patient by those further means of investigation unless other clinical features are suggestive of actual empyema. In other words, the existence of a serous effusion may be suspected, but never confirmed; its existence, proven or not, is regarded as unimportant until its undue persistence, or the appearance of other clinical features, give rise to serious suspicion of empyema.

In a different category, as far as hospital practice is concerned, is the sterile, serous effusion, proved by diagnostic aspiration, occurring in a patient who has not been observed from the beginning of his illness. Commonly such a patient has been ill at home for about 2 weeks, at the end of which the general practitioner, having originally diagnosed pneumonia, and having administered an adequate course of sulphonamide and/or penicillin, is disappointed and somewhat alarmed to find that the dullness in the chest is persisting or increasing and has begun to suspect empyema, neoplasm or tuberculosis. In such circumstances, the original diagnosis by the general practitioner must be accepted, in the interests of the patient, with some reserve. Thorough investigation is indicated. 11 cases of this type have been observed by the author (strictly speaking, 1 case should be excluded, since the effusion developed shortly AFTER admission to hospital, but for convenience in discussion, it has been included). The

11 cases are discussed initially in relation to important diagnostic features.

1. Radiological Evidence of Underlying Pulmonary Consolidation.

Of all diagnostic features, this is the most important, but it was present in only 4 of the 11 cases. In view of the time elapsing since the onset of illness and the previous treatment by the general practitioner, one would not expect it to be present in all cases. It is also possible for a large effusion to obscure the underlying lung; in only 1 of the 11 cases was the effusion large, and it may be that pneumonic serous effusions are commonly not large enough to trouble the radiologist in this way. Figures 82 - 84 are illustrations of particularly helpful X-rays from 2 of the 4 cases.

2. Clinical Evidence of Underlying Consolidation.

In 3 of the 4 cases with radiological evidence of consolidation, there was also clinical evidence of resolving consolidation - in the remaining case the consolidation affected the right middle lobe and was not detected clinically. In 1 other case, auscultation over the left lower lobe revealed numerous persistent coarse crepitations; this was taken to indicate inflammatory change, although the chest X-ray was unhelpful in confirmation.

3. Response of Pyrexia to Treatment.

All 11 patients had been treated prior to admission with sulphonamide and/or penicillin. 3 were



Fig. 82

Postero-anterior chest X-ray showing a loculated right pleural effusion with consolidation and some collapse of the right lower lobe. The effusion was serous, and sterile on culture. The patient, aged 35, had taken ill 3 weeks prior to admission to hospital and had been treated, as a case of pneumonia, with sulpha-thiazole. From the X-ray appearance, there could be no doubt that the effusion was simple inflammatory in origin. Both consolidation and fluid cleared with penicillin therapy. Bronchoscopy was not required.

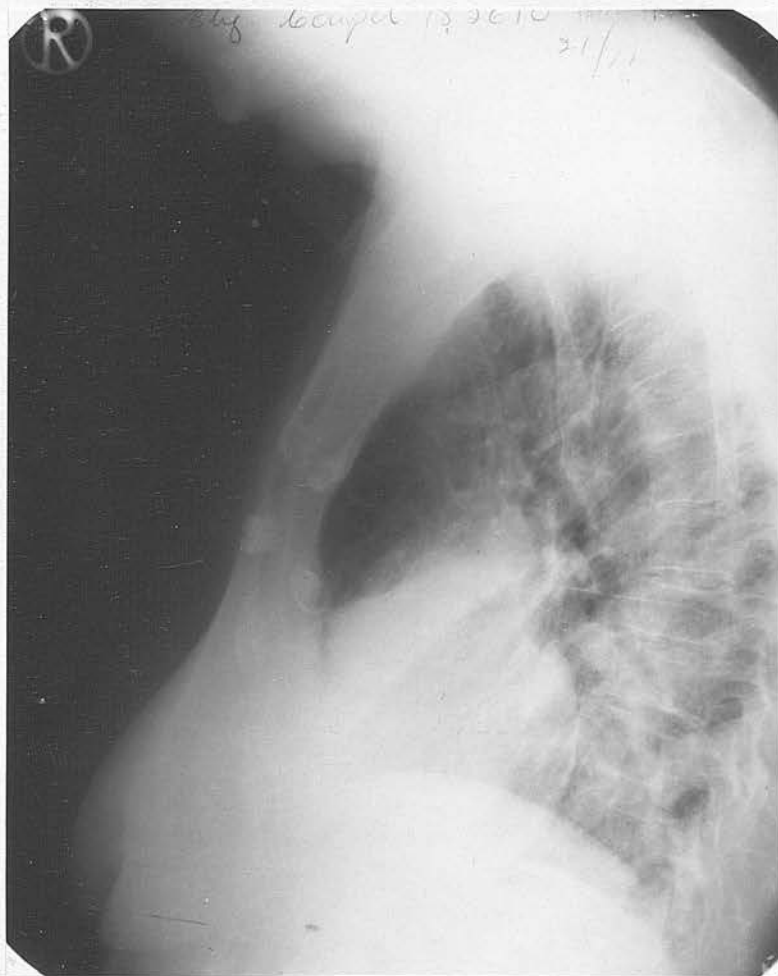


Fig. 83

Right lateral chest X-ray showing consolidation of the right middle lobe in a patient aged 50 who had been ill for nine days prior to admission to hospital. She had been treated with sulphonamide as a suspected case of pneumonia. On admission, clinical examination of the chest was negative. Penicillin therapy was instituted. Within a few days, stony dullness developed at the right lung base - see Figure 84.



Fig. 84

Right lateral chest X-ray (same case as Figure 83) 2 weeks later. The middle lobe consolidation has cleared; a pleural effusion is now present posteriorly. The fluid was serous, and sterile on culture. The radiological evidence strongly suggested a post-pneumonic effusion. Bronchoscopy was negative.

apyrexial on admission. The 8 pyrexial patients were treated with further penicillin and/or sulph-onamide. In 6 the pyrexia subsided, but not with sufficient rapidity to indicate a response to the treatment. In the remaining 2, the response was immediate and undoubted, and in 1 of the 2 a subsequent recurrence of pyrexia also responded immediately.

4. Negative Mantoux Test.

In 1 patient, apyrexial on admission and without radiological evidence of consolidation, the Mantoux Test (1:100) was negative and has remained so during a three year follow-up. This finding is taken to exclude a tuberculous aetiology, although otherwise, a diagnosis of primary tuberculous effusion would have had to be made.

5. Subsequent Course.

In three patients, the points already mentioned were unhelpful in establishing the diagnosis, but the subsequent course of events clarified the position.

i. The initial pyrexia subsided but subsequently became hectic with leucocytosis; eventual cure occurred with the coughing up of a large quantity of pus suggestive of pulmonary or pleuro-pulmonary abscess.

ii. Pyrexia and fluid persisted. After discharge to a convalescent home, the patient developed purulent sputum (negative for tubercle bacilli) and finger-clubbing; subsequent investigation revealed a bronchiectatic lower lobe on the side of the effusion. The lobe was resected at thoracotomy, which revealed no evidence of tumour or tuberculosis.

iii. Pyrexia persisted and originally clear effusion became turbid; subsequent resection of empyema space showed no pathological evidence of tuberculosis.

Less Important Diagnostic Features.

Referring to the problem of differentiating sterile, serous, simple inflammatory effusions from similar effusions due to other diseases, notably tuberculosis, Nairn (1949) states categorically that he has found the following investigations useless - total and differential white blood cell count, E.S.R., macroscopic appearance of fluid, biochemistry of fluid, cytology of fluid, and isolation of tubercle bacilli from fluid. He emphasises instead a careful review of the patient's history which may suggest that the original illness was pneumonic rather than primarily pleuritic. Trail (1943) emphasises the absence of pyrexia in effusions due to neoplasm, the clear eyes and skin of the tuberculous patient and the occasional presence of pleural eosinophilia in the post-pneumonic effusion. Maclean (1948) deprecates too much reliance on the cytology of the fluid; he suggests that a previous pleuritic incident in the past 6 months favours tuberculosis and that a polymorph leucocytosis in the peripheral blood favours simple inflammation.

On the whole, Nairn's conclusions seem reasonable. A polymorph leucocytosis in the peripheral blood may occur in the more acute forms of tuberculous pleurisy - as high as 21,000 per cu.mm. in one case observed by the author, while the white blood count is commonly normal - 10 of 11 cases - in previously treated pneumonia without actual empyema.

The E.S.R. is certainly worthless, being exceedingly variable in all types of pleural effusion. The macroscopic appearance of the fluid is the cause of the problem rather than a help in solving it, although subsequent aspirations may show a change to the turbidity of a frank empyema, in which case culture may no longer be sterile. The protein content of the fluid is high in simple inflammatory effusions, but this finding is common to all effusions other than transudates. The problem of cytology has already been discussed in Section II; in the individual case cytology is of little value, except that the rare finding of pleural eosinophilia favours simple inflammation rather than tuberculosis or neoplasm. The isolation of tubercle bacilli is dismissed too lightly by Nairn; it is in this type of problem case that the scheme suggested in Section III should be instituted; it is true that the results are not known for some time, but a positive finding, even if delayed, may prevent an error in diagnosis. The value of the patient's history depends upon his ability to recall the beginning of the illness after a lapse of time, although the accompanying letter from a helpful general practitioner may fill in deficiencies.

With regard to Trail's observations, it is true that the tuberculous patient, as opposed to the post-pneumonic patient, has clear eyes and skin; this, however, is a slender diagnostic point. Pyrexia may

be absent in post-pneumonic effusion - 3 of 11 cases - as well as in neoplastic effusion and, more rarely, in tuberculous effusion.

Maclean's point concerning a previous pleuritic incident in the past 6 months requires comment. In the author's experience it is exceedingly rare for a patient with a primary tuberculous effusion to give a history of a previous episode of pleurisy, or indeed illness of any kind, in the previous 6 months. The main characteristic of the illness is its explosive onset in a previously healthy person. In this respect, it would not seem to differ from pneumonia.

Sympathetic Effusion.

A sterile, serous, simple inflammatory pleural effusion is not always secondary to lung disease. It may result from infections of the subphrenic space and from suppurative amoebic hepatitis. Such an effusion is of significance only so far as it offers confirmation of sub-diaphragmatic infection.

Pleural Effusion in Virus Pneumonia.

Turner (1945) studied 286 cases of "primary atypical pneumonia" occurring in British service men in Italy during 1944. He states that 11 cases developed pleural effusion which was confirmed in 5 cases by diagnostic thoracentesis. 4 had yellow-green, semi-opaque sterile fluid and 1 had blood-stained sterile fluid; no other details of the fluid

are given.

Since the publication of Turner's paper, the author has reviewed specifically each case of pleural effusion encountered from the point of view of a causative virus pneumonia. In no case was there sufficient clinical or radiological evidence to justify such a diagnosis, or even to merit further investigation by means of serological tests. It must be admitted, however, that in a general hospital at the present time, virus pneumonia is rarely seen. Indeed there is an increasing reluctance among physicians to accept virus pneumonia, or at least "primary atypical pneumonia", as a definite clinical entity.

It would seem wise to keep an open mind on this problem. In epidemic conditions, such as observed by Turner, it may be reasonable to diagnose pleural effusion secondary to virus pneumonia. In ordinary hospital practice, however, the condition must be exceedingly rare, and should be diagnosed only in the presence of a clinical, radiological and serological picture highly suggestive of the existence of virus pneumonia. Even then it would be advisable to institute a follow-up regime on the assumption that the tubercle bacillus may be lurking in the background.

Practical Applications.

1. Sterile, serous pleural effusion complicating pneumonia presents no problem in aetiology provided

that the patient has been observed by the physician from the beginning of the illness. It is hard to estimate the frequency of such an effusion. Apart from progression to frank empyema, it is commonly of little importance.

2. In hospital practice, the patient may come under observation at a later stage in the illness, that is, as a case of sterile, serous pleural effusion for investigation. In those circumstances, it may be difficult to exclude primary tuberculous effusion and neoplastic effusion.

3. In establishing a diagnosis of simple inflammatory effusion, the author has found the following points of value -

i. Radiological, and to a lesser extent, clinical evidence of underlying pulmonary consolidation.

ii. Significant response of initial and subsequent recurrence of pyrexia to administration of penicillin and/or sulphonamide.

iii. Persistently negative Mantoux test, in so far as tuberculosis is excluded.

iv. Later complications - e.g. empyema.

v. The presence of pleural eosinophilia.

4. In the absence of such evidence, simple inflammatory effusion should not be diagnosed, even when the patient's history and/or information from the general practitioner suggest an initial pneumonic illness. The effusion should be regarded as tuberculous or

neoplastic, and appropriate steps taken to confirm or exclude those possibilities.

5. In younger patients particularly, this conservative approach to the problem may mean that the occasional case of simple inflammatory effusion will require to be regarded as a primary tuberculous effusion and followed up as such.

6. In older patients particularly, investigation for neoplasm may be indicated even when it is certain that the effusion is simple inflammatory in origin; the underlying lung consolidation may be secondary to neoplasm.

7. Pleural effusion due to virus pneumonia should not be lightly diagnosed.

SECTION IXPLEURAL EFFUSION IN PULMONARY INFARCTION

In a recent study of pulmonary infarction, Short (1951) found that, of 120 cases, 28 were complicated by pleural effusion. He does not imply that the pleural effusion was frequently an important part of the clinical picture; indeed, in most cases the effusion was small and detected only by radiological examination of the chest; in exceptional cases, the fluid was sufficient in quantity to half fill the affected hemithorax. Short's series of cases is unusual in that 96 of the 120 were subjected to chest radiology. In ordinary clinical practice, a patient with obvious pulmonary infarction is spared unnecessary movement - although perhaps less so than in the past - so that radiological examination and even diagnostic thoracentesis are rarely carried out. Short's figures showing the precise incidence of pleural effusion are therefore of great interest.

The author has observed in medical wards only 5 cases of significantly large pleural effusion complicating pulmonary infarction. 4 of the 5 cases were over 40 years of age and have already been reported in Section IV, page 129. Reference has also been made to 3 of the cases in Section II (pleural eosinophilia). It is now convenient to summarise important points relative to their diagnosis.

1. The Significance of Clinically Obvious Thrombophlebitis of the Leg Veins.

The pre-existence of obvious thrombophlebitis does not indicate with certainty that a pleuritic incident with pleural effusion is due to pulmonary infarction, although it is not unreasonable to connect the two. Thrombophlebitis may be the first manifestation of bronchial carcinoma - Fisher, Hochberg and Wilensky (1951) - and hence the pleural effusion may also be neoplastic in origin. In 2 of the 5 cases, there was obvious thrombophlebitis, but certain other features were initially suggestive of bronchial carcinoma, indicating that serious difficulty may arise over this apparently rather academic point.

2. Lack of Obvious Source of Embolus.

In 1 of the 5 cases, the diagnosis of pulmonary infarction (underlying a large pleural effusion) was not considered during life. At necropsy, an unsuspected cardiac infarction involving the right ventricle was found; a thrombus had formed inside the right ventricle and had become detached to cause a large pulmonary infarction. Clinically, bronchial carcinoma had been strongly suspected. An E.C.G. examination, had it been carried out, might have suggested revision of the diagnosis.

In 1 case, the presence of pelvic vein thrombosis could be assumed since the pulmonary infarction occurred in the puerperium.

In 1 case, there was little doubt that a pulmonary infarction had occurred although no obvious source of embolus was found. Since the episode occurred when the patient was confined to bed for other reasons, the leg veins seemed the probable source.

3. Radiological Examination.

In 4 of the 5 cases, there was no radiological abnormality of the chest other than the presence of pleural effusion. In the remaining case, only pleural effusion was seen initially, but absorption of the fluid revealed a clearing opacity in the right lower lobe consistent with a pulmonary infarction. Short (1951) comments on the failure of radiology to establish a diagnosis of pulmonary infarction in the presence of obscuring effusion.

4. Haemoptysis.

4 of the 5 patients had haemoptysis, but in 3 the pleural effusion preceded the haemoptysis. While haemoptysis is rare in primary tuberculous effusion, bronchial carcinoma is again the problem in differential diagnosis.

5. Characters of the Fluid.

1. Blood-staining.

Only 2 of the 5 fluids were haemorrhagic. This is in keeping with Short's series in which 8 of 28 fluids were haemorrhagic.

ii. Protein Content.

All 5 fluids had a high protein content.

iii. Cytology.

Reference has already been made to cytology in Section II. There is a tendency for the Pathologist to diagnose malignant cells in error. Well marked pleural eosinophilia was present in 3 cases.

Practical Applications.

1. Pulmonary infarction is a comparatively rare cause of significantly large pleural effusion.
2. When a large pleural effusion occurs, it may cause a diagnostic problem because of the close resemblance of many of the features to those of malignant disease, especially bronchial carcinoma.
3. The site of origin of the causative embolus may not be obvious. An E.C.G. examination, apart from showing features of actual pulmonary infarction, may reveal an unsuspected cardiac lesion from which a pulmonary infarction may have resulted.
4. The pre-existence of thrombophlebitis of the leg veins is a strong point in favour of pulmonary infarction, although it is theoretically possible for both pleural effusion and thrombophlebitis to result from bronchial carcinoma. It is probable that a patient with pleural effusion and thrombophlebitis is not fit for bronchoscopy and thoracoscopy, and should therefore be treated with anti-coagulants in the hope

that the obvious diagnosis of pulmonary infarction is the correct one.

5. The finding of pleural eosinophilia may be helpful. While not diagnostic of pleural fluid due to pulmonary infarction, it is strongly against a diagnosis of neoplasm.

SECTION XINVESTIGATION OF A PATIENT PRESENTING
WITH SEROUS PLEURAL EFFUSION

In order to avoid a morass of detail in the presentation of this section, certain problems have been discussed separately in previous sections. In Sections II and III the value of cytological and bacteriological investigation has been indicated. In Section IV it has been shown that primary tuberculous pleural effusion is not uncommon in older age groups. In Sections V to IX serous pleural effusion due to cardiac failure, collagen disease, reticulosis, simple inflammation and pulmonary infarction has been discussed in detail with special reference to diagnostic difficulties which may arise.

From the point of view of the Physician practising in a general hospital, the presentation may be further simplified, at least initially, by concentrating on his most common, and at the same time, most anxious problem for investigation. This is not the younger age group patient in whom the effusion is nearly always tuberculous in origin. It is the older age group patient with effusion not due to obvious disease of the lungs, heart or elsewhere, in whom, among less common and less important causes, tuberculosis and neoplasm require equal consideration and, as quickly as possible, differentiation.

Reference to Section IV, page 122, will indicate how 73 older age group patients with pleural effusion of initially uncertain aetiology were selected. Ultimately, 24 proved to have primary tuberculous effusion and 24 proved to have neoplastic effusion; of the 24 neoplastic cases, 15 had bronchial carcinoma and 9 primary carcinoma elsewhere in the body. The 48 cases are now analysed with respect to important differentiating clinical features.

TABLE 27

Pleural Effusion of Initially Uncertain Aetiology
Important Clinical Features in Patients
over 40 Years of Age

Clinical Feature	Ultimate Aetiology	
	Neoplastic (24 cases)	Tuberculous (24 cases)
Pain - Typical Pleuritic	7	17
Boring	2	0
Aching	1	1
Anginal	1	0
Vague Abdominal	1	0
NONE	12	6
Haemoptysis	3	0
Finger Clubbing	6	0
Fluid Blood-stained	10	1
Rapid Recurrence of Fluid after Aspiration	10	0

TABLE 28 /

TABLE 28Pyrexia During First Week in Hospital

Degree of Pyrexia	Ultimate Aetiology	
	Neoplastic (24 cases)	Tuberculous (24 cases)
Nil	18	2
Occasional to 99°F.	3	5
Regular to 100°F. or over	3	17

Comments on Tables 27 and 28.

Pain. In the neoplastic patient, pain is commonly absent from the history; if present, it may be of a particularly unpleasant "boring" type continuing after the formation of effusion. In the tuberculous patient, pain is commonly present and is typically pleuritic in type disappearing with the formation of fluid.

Haemoptysis. In the form of streaking of sputum, this occurred in 3 patients with bronchial carcinoma. According to Karron and Purves (1947) haemoptysis may occur in 7% of patients with primary tuberculous effusion; examination of their data suggests, however, that at least some of their patients had actual tuberculous infiltration of the lungs - i.e. the effusion was not always "primary". The author has observed only 1 instance of haemoptysis in 100 patients with primary tuberculous effusion.

Finger Clubbing. The 6 patients with this finding all proved to have bronchial carcinoma.

Blood-staining of Fluid. The figures refer only to initial diagnostic aspiration. It is well known that blood-staining may occur occasionally in tuberculous effusion.

Rapid Recurrence of Fluid After Aspiration. By this is meant massive recurrence in the course of the next 24 hours. It must be rare for a tuberculous effusion to re-accumulate with such rapidity. In general, it was the haemorrhagic neoplastic fluid which showed this characteristic.

Pyrexia During First Week in Hospital. The figures are self-explanatory. A minor degree of pyrexia is common to both neoplastic and tuberculous patients. The 3 neoplastic patients with major pyrexia require further comment: 1 proved to have deposits of malignant melanoma in the lungs from an undetermined primary site; 2 proved to have bronchial carcinoma, and in 1 of those further observation of the temperature chart showed a Pel-Ebstein type of pyrexia. Bronchial carcinoma may, of course, cause pyrexia by virtue of inflammatory complications - pneumonia, lung abscess, bronchiectasis, empyema; in those 2 cases, however, there was no obvious evidence of such complications; presumably the pyrexia was due to the tumour per se.

A further point of importance is the relation of

pulse rate to temperature. In all the tuberculous patients, the pulse rate was elevated to a degree corresponding to the degree of pyrexia - in the 2 apyrexial patients the pulse rate was normal. In the neoplastic patients, there was nearly always a relative tachycardia; most significantly, of 18 apyrexial patients, 11 had a pulse rate of over 100 per minute; it may be that this finding is due to the inability of mediastinum and heart to accommodate to the comparatively rapid formation of neoplastic fluid.

Apart from the clinical features analysed in the tables, reference must be made to the state of health of patients in the few months preceding the pleural episode necessitating admission to hospital. With only 1 exception, the tuberculous patients would not admit to any manifestation of ill-health leading up, as it were, to the final illness; this patient complained of vague malaise. In contrast, of the 24 neoplastic patients, 19 had complained of ill-health of some kind. In the bronchial carcinoma group the complaints were of cough, dyspnoea on exertion, "influenza", mild pneumonia, obscure malaise with slight fever, and vague discomfort in the affected side of the chest. In the "other carcinoma" group, the main complaint was of weight loss, although dyspnoea on exertion, easy fatigue and dyspepsia were

also mentioned. From those details a general principle emerges: in the older person, as in the young adult, primary tuberculous effusion is usually not preceded by a period of ill-health, forming in this respect a marked contrast to neoplastic effusion.

Radiological Examination of the Chest: From the nature of the 48 cases under consideration, i.e. those with pleural effusion not due to obvious disease of the lungs, heart or elsewhere, it follows that radiological examination of the chest was not helpful initially in establishing the diagnosis. The actual X-ray reports, based on postero-anterior, lateral and Bucky films, can be summarised in tabular form.

TABLE 29

Pleural Effusion of Initially Uncertain Aetiology

Report on Chest X-ray

Report	Ultimate Aetiology		
	Bronchial Ca. (15 cases)	Other Ca. (9 cases)	Tuberculous (24 cases)
Fluid Only	11	7	19
" + Hilar Gland	2	0	1
" + ?Atelectasis	2	1	2
" + Rounded Opacity	0	1	1
" + Big Heart	0	0	1

Comments on Table 29.

Fluid Only. No comment required.

Fluid + Hilar Gland. While hilar gland enlargement may occur with primary tuberculous effusion, it has been emphasised - Section IV - that it is distinctly uncommon in older patients. This finding should therefore be regarded as highly suspicious of bronchial carcinoma.

Fluid + ?Atelectasis. The figures are interesting. It is clear that suspected atelectasis does not necessarily indicate bronchial carcinoma. It may be said that atelectasis is difficult to diagnose radiologically in the presence of obscuring fluid, and that there is, among radiologists, a tendency to suggest atelectasis when its existence is perhaps doubtful. In none of the 5 cases was there clear cut evidence of mediastinal shift TOWARDS the side of the fluid, which is probably the only unequivocal sign of atelectasis in the presence of fluid.

Fluid + Rounded Opacity. While the presence of a rounded opacity or rounded opacities in the lung fields must give rise to serious suspicion of neoplasm, particularly secondary neoplasm, difficulties in interpretation may arise. Figures 85 to 87 illustrate the appearances in the 2 cases with this finding. One case proved to be tuberculous and the other neoplastic (secondaries from carcinoma of stomach).

Fluid + Big Heart. In older patients, cardiac enlargement may have no connection with the pleural



Fig. 85

Postero-anterior chest X-ray of Mrs. J.W. aged 51 taken after aspiration of the left pleural cavity. In addition to residual fluid, there is a rounded opacity overlying the 3rd left anterior rib. The opacity proved to be due to a secondary deposit in the lung from a primary gastric carcinoma. From the radiological point of view, it was not possible to diagnose the nature of the opacity, although secondary neoplasm was strongly suspected.

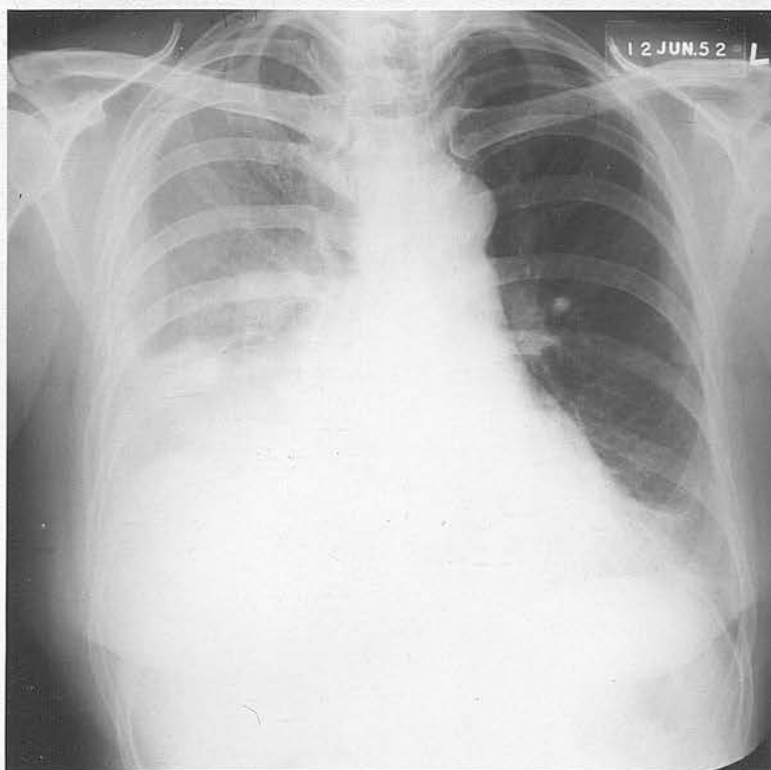


Fig. 86

Postero-anterior chest X-ray of Mrs. H.C. aged 65 taken on 12. 6.52 after aspiration of the right pleural cavity. In addition to residual fluid and generalised hazing of the right lung field, two rounded opacities are seen overlying the 7th and 8th right posterior ribs. Secondary neoplasm was strongly suspected (see also Fig. 87).

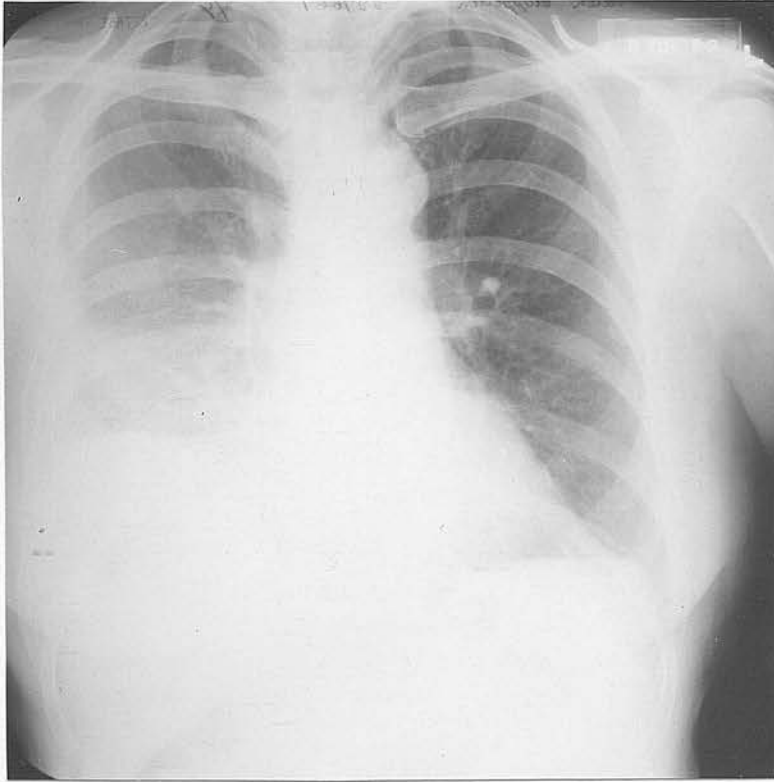


Fig. 87

Same patient as Figure 86 on 8. 7.52, i.e. 26 days later. The rounded opacities are no longer visible. The patient eventually died of miliary tuberculosis. It is possible that the initial opacities represented loculated collections of fluid.

effusion.

It should be noted that tomography was not available in the hospital in which the patients were investigated. Screening of the diaphragmatic movement for neoplastic paralysis of the phrenic nerve was not carried out in any of the patients; this, in relation to modern methods of chest investigation, is perhaps a serious omission, although it is probable that in this series little further positive information would have been obtained.

Suggested Scheme of Investigation in the Older Age Group Patient with Serous Pleural Effusion.

This scheme, applicable to the general physician, is based on information derived from

- (a) a retrospective clinical study of the 48 patients analysed in this section.
- (b) previous sections, particularly those relating to cytological and bacteriological investigation.

1. Little investigation may be required if the patient has obvious clinical or radiological evidence of malignant disease in the lungs or elsewhere, or obvious radiological evidence of the "adult" form of pulmonary tuberculosis. Such investigation will consist largely of measures - e.g. bronchoscopy, lymph gland biopsy, Barium X-rays, sputum examination for tubercle bacilli - designed to confirm an

already almost certain diagnosis so that appropriate disposal and, if possible, treatment of the patient may be arranged with a minimum of delay.

2. If malignant disease and the "adult" form of pulmonary tuberculosis are not obviously present, consideration, as outlined in previous sections, should be given to unusual forms of cardiac transudate, collagen disease, reticulosis, simple inflammation and pulmonary infarction. Appropriate investigations for those conditions may be required. Meig's Syndrome may be included in this group.

3. Although many patients may be eliminated from the "problem" list under para. 1, and a few may be eliminated under para. 2, many will be left for further investigation to determine whether the effusion is primary tuberculous or due to cryptogenic neoplasm. It is suggested that a careful study of relatively simple clinical points may enable a reasonably certain differentiation to be made. An illness characterised by sudden onset of typical pleuritic pain in a previously healthy person and associated with a high degree of pyrexia during the first week in hospital is highly suggestive of a tuberculous background - i.e. the clinical picture in the older person does not differ from that in the younger person. On the other hand, an illness characterised by preceding ill-health, which may be manifested in diverse ways, leading up to insidious development of pleural

effusion is highly suggestive of a malignant background, especially if associated with one or more of the following features - "boring" chest pain, finger clubbing, slight haemoptysis, haemorrhagic fluid, rapid recurrence of fluid and absence of pyrexia with relative tachycardia during the first week in hospital.

4. In the absence of helpful information from radiological examination of the chest, there is probably only one other immediately useful means of investigation available to the physician. This is cytological examination of the pleural fluid, which may confirm malignancy - see Section II - if there is present -

(a) A very high proportion of "serosal" cells in the Leishman film.

(b) Actual malignant cells in the H. and E. section. It cannot be too strongly emphasised that a predominantly lymphocytic cytological picture is common to both tuberculous and malignant fluids.

(It is convenient to mention at this point the estimation of the glucose content of the pleural fluid of which the author has no personal experience. Calnan, Winfield, Crowley and Bloom (1951) found that a glucose level of less than 60 mgms. per 100 mls. occurred only in tuberculous fluids. In view of its potential value as a rapid means of assessment, glucose estimation requires further clinical trial).

5. Less helpful from the point of view of immediate results are measures - Section III - for the efficient isolation of tubercle bacilli from the fluid and sputum (or gastric juice). It is suggested, nevertheless, that those measures should be instituted in every case since they may provide, in the course of time, confirmation of a presumptive diagnosis of tuberculosis, and may even solve a diagnostic problem resisting all other methods of investigation.

6. Fortunately, diagnostic facilities, especially bronchoscopy and thoracoscopy, are now becoming more widely available to general hospitals with the development of thoracic surgical units throughout the country. In the investigation of pleural effusion, the help of the thoracic surgeon is frequently essential. This does not mean that every older age group patient with pleural effusion should be subjected to "surgical" investigation. The following points should be kept in mind.

(a) Bronchoscopy and thoracoscopy are somewhat unpleasant procedures for the patient.

(b) Thoracic units are coping with an enormous volume of work which should not be added to unnecessarily.

(c) If the patient is acutely ill with a tuberculous effusion, bronchoscopy and thoracoscopy certainly do him no good and may indeed worsen his condition.

(d) If the effusion is in fact malignant, the proof of this afforded by bronchoscopy and/or thoracoscopy is commonly of little value to the patient, since radical treatment of the malignant condition is usually, although not always, impossible because of the pleural involvement.

From the practical point of view, it seems reasonable to decide for or against "surgical" investigation as follows -

i. If the clinical study - para. 3 - and/or cytological examination of the fluid favour a malignant background, "surgical" investigation should be arranged without delay so that the patient may be given his faint chance of successful radical treatment on the establishment of the diagnosis.

ii. If the clinical study favours a tuberculous background and cytological examination of the fluid is consistent, "surgical" investigation should be withheld or at least delayed. It has been shown - Section IV - that primary tuberculous effusion in the older person is a potentially grave condition, probably meriting immediate treatment with modern anti-tuberculosis drugs. A course of streptomycin and para-amino-salicylic acid (P.A.S.) should be instituted, and its effect on the clinical state, especially the pyrexia, observed - Figures 88 and 89.

iii. A review of the author's cases suggests that few errors of procedure will occur with this method

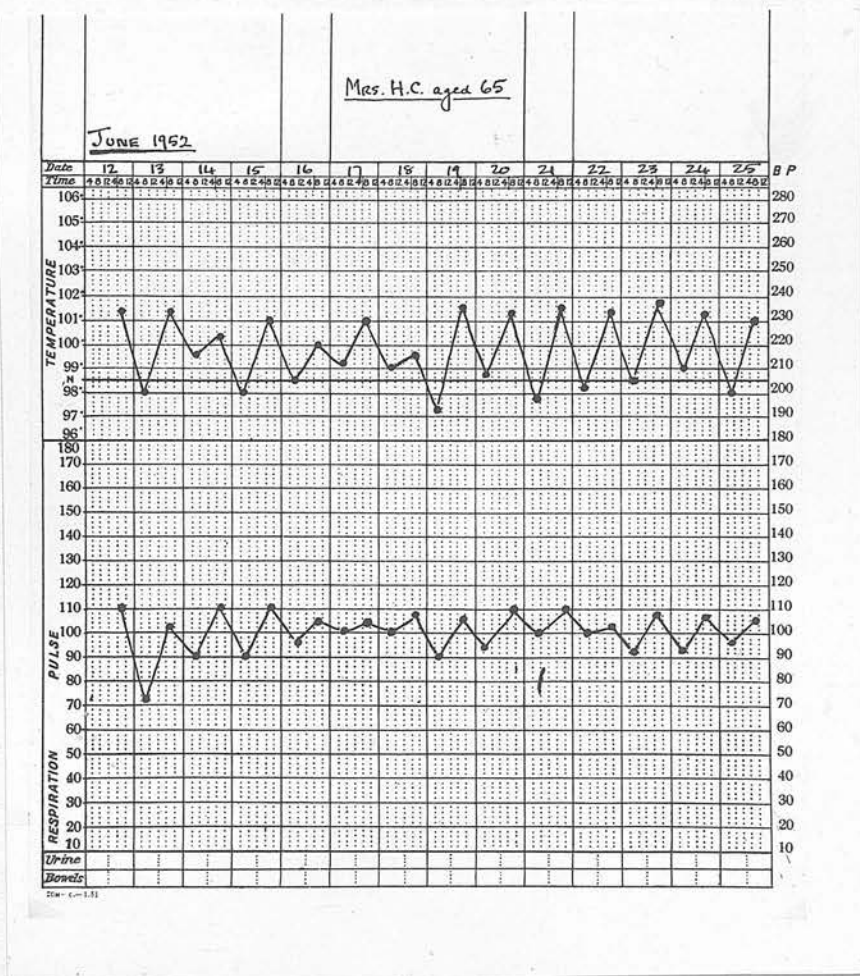


Fig. 88

Mrs. H.C. aged 65 was admitted to hospital on 12. 6.52. She had a serous pleural effusion on the right side. The clinical study was highly suggestive of a tuberculous illness, but X-ray of chest - see Fig. 86 - showed in the right lung field two rounded opacities which gave rise to erroneous suspicion of secondary neoplasm. The chart of her first two weeks in hospital is reproduced (see also Fig. 89).

of decision. The occasional tuberculous patient with an illness characterised by insidious onset and absent pyrexia will be sent for "surgical" investigation because of those malignant-like features. The very occasional malignant patient - e.g. the patient with malignant melanoma referred to in Table 28 - because of acute pleuritic illness, high pyrexia and lack of other features suggestive of malignancy, will be wrongly treated initially as a case of tuberculosis; in this event, the patient has probably lost nothing and has been given his only chance of gain by assuming that he had a "treatable" condition, namely tuberculosis.

7. It is hardly necessary to state that the final method of investigation is continued observation of the patient in whom a provisional diagnosis of tuberculosis has been made. If the diagnosis is correct, clinical improvement should eventually occur, especially under the influence of streptomycin and P.A.S. therapy. If it does not, the decision to withhold "surgical" investigation may require review. The possibility of tuberculosis and malignant disease co-existing should also be kept in mind.

Investigation of the Young Adult with Serous Pleural Effusion.

At the beginning of this section, it was stated that nearly all serous effusions in younger age group

patients are tuberculous in origin. Of 85 consecutive patients under the age of 40 years - actual

	12 to 19 - 45	
age incidence -	20 to 29 - 32	- admitted to two med-
	30 to 39 - 8	

ical charges in the Royal Infirmary of Edinburgh for investigation of serous pleural effusion, 76 (89.4%) had ultimately nothing in the clinical, radiological, bacteriological or follow-up picture to suggest a diagnosis other than primary tuberculous effusion; since many were included in the bacteriological investigation described in Section III, the isolation rate for tubercle bacilli was particularly high. In 2 further patients, the chest X-ray revealed extensive pulmonary tuberculosis of the "adult" type, bringing the total of tuberculous cases to 78 (91.8%).

The remaining 7 patients proved to be non-tuberculous -

Post-pneumonic serous effusion	- 3
Malignant (carcinoma of breast)	- 1
Trauma	- 1
Pulmonary Infarction	- 1
Transudate from acute rheumatic carditis	- 1

In all 7 the correct diagnosis was easily and quickly established with a minimum of investigation - history, clinical examination, diagnostic thoracentesis and X-ray of chest; in 2, a persistently negative Mantoux test confirmed the absence of tuberculosis.

Although it has been stated above with respect to the 76 patients with primary tuberculous effusion that there was ultimately nothing to suggest an alternative diagnosis, in 4 patients there was initial difficulty due to some deviation from the usual clinical picture.

(1) See case 6, Section VI, page 177. In this patient, a suspicion of rheumatic pleurisy existed because of a previous episode of pericarditis erroneously diagnosed as rheumatic.

(2) See case 7, Section VI, page 178. In this patient, a suspicion of rheumatic pleurisy existed because of associated muscular pains and pericarditis in addition polymorph leucocytosis in the peripheral blood and polymorphous exudate in the pleural fluid seemed against a tuberculous aetiology.

(3) A male patient aged 19 was admitted with severe toxaemia and left pleurisy with effusion. The fluid was clear and serous, sterile on culture and predominantly polymorphous. Although no other aetiology was obvious, tuberculosis was considered unlikely because of the polymorphous fluid and a negative Mantoux test (1:100). The Mantoux test eventually became positive after 9 weeks, during which toxaemia remained severe. The patient died of meningeal and miliary tuberculosis.

(4) A male medical student aged 22 developed an

acute right pleurisy with effusion. After admission to hospital he was found to have a moderate irregular pyrexia, but the pulse rate never exceeded 70 per minute - he stated that his normal pulse rate was 50 per minute. Diagnostic aspiration revealed a clear, serous fluid, sterile on culture and predominantly polymorphous. The X-ray of chest was said to show a right pleural effusion with "some atelectasis" of the right lower lobe; there was no evidence of a primary tuberculous complex. During the course of three weeks, the fluid increased in quantity; it remained clear and sterile; the polymorphous exudate became lymphocytic. At this point, he had a slight haemoptysis. The provisional diagnosis had been tuberculosis, but a review of the case gave rise to some anxiety because of unusual features -

- (a) relative bradycardia
- (b) originally polymorphous exudate
- (c) "some atelectasis" of the right lower lobe
- (d) haemoptysis in the absence of an obvious tuberculous lung lesion.

It was felt that bronchial adenoma or even bronchial carcinoma could not be excluded. Bronchoscopy showed no abnormality of the bronchial tree. Subsequently the pyrexia subsided and the fluid absorbed slowly. Follow-up X-ray of chest 2 years later

showed normal lung fields. Although no bacteriological proof was obtained, the weight of evidence, both positive and negative, favoured a tuberculous aetiology.

Those 4 exceptional cases indicate the nature of features which tend to confuse the physician, so leading the diagnosis away from tuberculosis. In summary, the features are

- (a) polymorphous exudate in fluid
- (b) associated pericarditis
- (c) "rheumatic" pains
- (d) radiological suspicion of atelectasis
underlying fluid
- (e) polymorph leucocytosis in peripheral blood
- (f) negative Mantoux test
- (g) haemoptysis in the absence of an obvious
tuberculous lung lesion.

It has been shown in Section II that a polymorphous exudate in the fluid is not excessively rare in tuberculosis. Associated pericarditis and "rheumatic" pains inevitably raise the suspicion of a rheumatic process, but tuberculous pericarditis and "tuberculous rheumatism" should not be forgotten. Definite atelectasis may be due to bronchial compression from tuberculous hilar lymphadenopathy; this type of bronchial compression, although not

uncommon in children, has not been observed by the author in young adults, and therefore bronchoscopy is indicated to exclude other pathology. If a tuberculous effusion has a polymorphous exudate, it is not unreasonable to expect a polymorph leucocytosis in the peripheral blood. A negative Mantoux test occurred in only 1 of the 76 primary tuberculous patients; he eventually died of meningeal and miliary tuberculosis; although a negative test is very strong evidence against tuberculosis, the existence of the occasional exception calls for caution in interpretation. Haemoptysis is a rarity in primary tuberculous effusion.

In conclusion, it may be stated that in the young adult with serous pleural effusion, investigation beyond the routine of history, clinical examination, diagnostic thoracentesis, X-ray of chest, observation of temperature chart and possibly Mantoux test is seldom required for the purpose of establishing the aetiology. The probability of a tuberculous aetiology is so great that unusual and, at first sight, apparently incompatible features should be interpreted with some reserve. Occasionally, however, genuine difficulty may arise, necessitating investigation in precisely the same manner as in the older patient, including measures for the efficient

isolation of tubercle bacilli and possibly even bronchoscopy and thoracoscopy. A neoplastic background is not excluded by age alone. Serous effusion of post-pneumonic origin is probably very uncommon in the young adult. Certainly it cannot be diagnosed to the exclusion of tuberculosis unless there is unequivocal radiological evidence of resolving lung consolidation and/or a negative Mantoux test remaining negative far into convalescence.

SECTION XIPROGNOSIS IN PRIMARY TUBERCULOUS PLEURAL EFFUSION

This section is not concerned with pleural effusion occurring as a complication of the "adult" form of pulmonary tuberculosis. Nor is it concerned with what might be called the "local" complications of primary tuberculous pleural effusion; no doubt in the past death has occurred from failure to aspirate a massive effusion, and on occasions even now troublesome situations may arise from secondary infection of the fluid, ill-advised air-replacement of the fluid and, perhaps least uncommon of all, residual fibrosis of the pleura. By and large, however, those local complications are rare and comparatively unimportant. To the patient and his medical advisers, it is the ultimate prognosis, with respect to the development of overt tuberculosis in the lungs or elsewhere, which really matters.

The exact incidence of subsequent overt tuberculosis is difficult to establish because of considerable divergence of morbidity figures in the literature. Table 30 gives a selection of series published since 1940.

TABLE 30 /

TABLE 30

Primary Tuberculous Pleural Effusion
Varying Tuberculous Morbidity in Different Series

Year	Author(s)	Country	No. of Cases	T.B. Morbidity Per Cent
1940	Vaizey & Perry	England	308	30.0 (app.)
1941	Schuman	U.S.A.	214	17.7
1942	Bonilla	U.S.A.	70 ⁽¹⁾	40.0
1943	Farber	U.S.A.	137	29.0
1944	Robson	England	111	23.0 ⁽²⁾
1945	Fauvet	France	731	12.8
1946	Conybeare	England	84	12.0
1946	Nilsen	Norway	138	12.3
1946	Jervell & Istre	Norway	143	7.7
1946	Thompson	England	190	21.1
1949	Kraft	U.S.A.	100	21.0
1949	Landau	England	54	11.0
1949	Kennedy & Melrose	Scotland	48	7.5
1951	Frostad	Scandinavia	720	20.6

Note (1) Included both black and white patients.

Note (2) Excluded minimal X-ray changes in the lungs.

Series published prior to 1940 tended to show even higher morbidity rates, but the lessening virulence of tuberculous infection throughout the world

during the intervening years makes them of less importance to the argument at the present time.

Maclean (1948) has already analysed the possible reasons for the divergent figures. Among them may be mentioned geographical factors, inclusion of patients with "adult" pulmonary tuberculosis, misdiagnosis of malignant effusions, method of follow-up, attitude to untraced patients, age distribution of patients, social status of patients and method of treatment.

In view of the divergent figures, it is considered justifiable to add yet another series to those already published. The author's series may be taken to represent the position as it existed in a general hospital - Royal Infirmary of Edinburgh - in Scotland in the years (1945 - 1950) immediately prior to the general use of antibiotic and chemotherapeutic agents in the treatment of tuberculosis. The 100 patients in the series were observed from the time of the initial illness and followed-up personally by the author. It is reasonably certain that no misdiagnosis occurred; clinical and radiological follow-up is virtually complete over a period of 3 to 8 years. The only apparent flaw in the series lies in the fact that, although the patients were consecutive admissions, 5 medical charges were used to obtain a larger number of "scarce" patients over 40 years of age, whereas only 2 of the 5 charges were used for

the "under 40" patients. It would have proved too large a task to maintain personal supervision over all the "under 40" patients from all 5 charges. So that the reader may appreciate the precise extent of this flaw, the "over 40" and "under 40" patients are analysed, in the first instance, separately - Table 31.

TABLE 31

Primary Tuberculous Pleural Effusion

Subsequent Tuberculous Morbidity
and Mortality in 100 Patients

	Under 40 ⁽¹⁾ (76 Patients)	Over 40 (24 Patients)
Alive and Well	55	11
Untraced	1	0
Dead - Unrelated Cause	0	2
Pulmonary Tuberculosis	15 ⁽²⁾ } 20	7 } 11
Non-Pulm. Tuberculosis	5 } 20	4 } 11
	<u>76</u>	<u>24</u>
Dead - Tuberculosis	4	6
	<u>Per Cent</u>	<u>Per Cent</u>
Tuberculous Morbidity	26.3	46.0
Tuberculous Mortality	5.3	25.0

Note (1) Actual Age incidence

	Years	
12 - 19	:	43
20 - 29	:	29
30 - 39	:	4

Note (2) Includes one patient with progressive primary focus in lung, and two patients who eventually developed non-pulmonary lesions as well.

Combining the two age groups, and therefore weighting the figures with the RELATIVELY greater number of older patients in whom the prognosis appears to be more serious, the results become

Tuberculous Morbidity - 31.0%.

Tuberculous Mortality - 10.0%.

It should be noted that the mortality rate is at a minimum level, since it is probable that some of the patients at present being treated for active tuberculosis will eventually die of their disease.

This follow-up series confirms the potential gravity of primary tuberculous effusion as it occurred towards the end of the 1940-1950 decade. The British Medical Journal (1946) stated that there was still doubt about the prognosis, but that the available evidence pointed to an incidence of overt tuberculosis of "over 30%" in persons between the ages of 15 and 40. The author's figures are in substantial agreement with this estimate.

Prognosis in the Individual Patient.

While the literature abounds with series of patients showing over-all morbidity and mortality rates, few authors have attempted the difficult and perhaps impossible task of analysing factors which influence prognosis and which may be assessed at the time of the original illness, thus giving the Physician an indication of which particular patient is likely to "go wrong". Reasons for this dearth

of information are not difficult to find -

1. Many series have been followed-up at chest clinics by physicians who did not have access to the clinical records of the original illness - e.g. Thompson (1946). In those circumstances, it is obviously impossible to assess prognostic factors in retrospect.
2. Because of the relatively small number of patients developing overt tuberculosis, a statistically significant analysis of factors influencing prognosis would require follow-up of a very large number of patients from the time of the original illness. This ideal is not available to the individual worker.
3. Assessment of factors present at the original illness tends to be rendered inaccurate or even misleading by the influence of factors in the convalescent and follow-up periods - e.g. length of period of convalescence, social circumstances, co-operation of patient in leading a restricted life.
4. Finally, the Physician may feel that attempts to prognosticate in the individual patient are a waste of time. Thus Laurie (1950) states "--- it is policy to treat every case as potentially tuberculous, because only by so doing can the secondary lesions be detected at a stage where it is possible to treat them; there is no infallible prognostic guide which spares us this obligation and the treatment of an effusion seems to matter little; the most

carefully managed pleurisy may still develop secondary lesions".

There is no question of disagreement with Laurie's statement, but again there is no mention of trying to select the bad risk patient for special attention and treatment. It is true that in the past, selection of such a patient would have meant, at most, only a more protracted convalescence under sanatorium conditions. Is it possible that at the present time more could be done for the bad risk patient, given that he could be selected? It seems reasonable to postulate that more MIGHT be done in the form of modern anti-biotic and chemotherapy directed against the tubercle bacillus. With this postulate in mind, it seemed to the author worth while to attempt a review of prognostic factors in the hope that the results might be applied to the treatment of patients in the future.

Review of Prognostic Factors.

1. Age of Patient.

This has been considered in detail in Section IV. There is definite evidence that in children the prognosis is relatively good and suggestive evidence that in adults over 40 years of age the prognosis is relatively bad. It should be noted, however, that in the author's "over 40" patients, the extraneous factor of inadequate convalescence may have played a part in worsening the prognosis.

2. Bilateral Pleurisy with Effusion.

The incidence of bilateral - simultaneous or consecutive - pleurisy with effusion varies in different series: Erwin (1944) - 13%; Bird (1946) - 14.6%; Thompson (1946) - 4.8%; Karron and Purves - (1947) - 7.5%. Of those authors, only Thompson has a satisfactory follow-up investigation, but certain other authors have reported on the follow-up of selected cases of bilateral effusion which have come under their care, mostly in sanatoria. Fernandes (1944) observed in the Derbyshire Sanatorium 5 cases of which 4 developed miliary tuberculosis and 1 developed tuberculosis of the spine with tuberculous enteritis. Paine (1941) observed a larger series of 24 cases in a sanatorium in the United States; of the 24, 18 (75%) developed tuberculosis in the lungs and/or elsewhere. Thompson (1946) had 9 cases in his series of 190 patients; of the 9, 4 developed tuberculosis in the lungs or elsewhere. Hurrell and Dawson-Walker (1939) and Gray (1940) have each reported a single case of bilateral effusion progressing to fetal miliary tuberculosis.

Fernandes, quoting his own experiences and those of Hurrell & Dawson-Walker and Gray, believes that bilateral pleurisy with effusion may be an early manifestation of miliary tuberculosis, although the effusions may appear to be primary because of the masking and retarding effect of lung compression

on the radiological appearances. Paine comments on the high incidence of extra-pulmonary lesions in his cases indicating that haematogenous dissemination - if not actually miliary tuberculosis - is likely to occur following, or perhaps has already occurred at the time of, the effusions. Paine also refers to 21 cases in which the effusions were secondary to established pulmonary tuberculosis and points out that the mortality rate was actually less in those cases than in the 24 without detectable pulmonary lesions. Further, he found that in the latter group, a long interval between consecutive effusions did not improve the prognosis with respect to either morbidity or mortality. 5 cases of consecutive bilateral effusion occurred in the author's series. Only 1 developed overt tuberculosis - in the lungs, but 2 were treated with streptomycin, which had just become available, because of the apparent risk of miliary tuberculosis.

It is clear that further investigation is required on the problem of bilateral pleurisy with effusion, preferably with co-operation among several groups of workers so that a reasonable number of cases can be collected. There is, however, suggestive evidence that simultaneous or consecutive involvement of both pleural cavities worsens the prognosis and may lead to - or perhaps is the result of - haematogenous dissemination or actual miliary tuberculosis.

3. Duration of Pyrexia.

A search of the literature has revealed only one instance of an attempt to base prognosis on duration of pyrexia. This is in the series reported by Maclean (1948). Unfortunately, the duration of pyrexia was not known in all of his cases, but he constructs the following table -

<u>Duration (Weeks)</u>	<u>No. of Cases</u>	<u>No. developing Tuberculosis</u>	<u>Tuberculous Morbidity (Per Cent)</u>
0 - 3	35	6	17.1
3 - 6	39	5	12.8
6 - 11	17	7	41.2
Over 11	21	7	33.3
Unknown	44	7	15.9
OR			
0 - 6	74	11	14.9
Over 6	38	14	36.8
	<hr/>	<hr/>	
	112	25	
	<hr/>	<hr/>	

In the author's series of 100 cases, the average duration of pyrexia - temperature recorded in all cases in the axilla - was much shorter than in Maclean's series, and it is therefore convenient to take 4 weeks rather than 6 weeks as the dividing line.

<u>Duration (Weeks)</u>	<u>No. of Cases</u>	<u>No. developing Tuberculosis</u>	<u>Tuberculous Morbidity (Per Cent)</u>
0 - 4	85	23	27.1
over 4	15	8 ⁽¹⁾	53.3
	<hr/>	<hr/>	
	100	31	
	<hr/>	<hr/>	

Note (1) In addition to the 8 cases, 2 more sub-

sequently developed pleurisy with effusion on the contralateral side, which, in relation to the previous discussion, might be regarded as a potentially serious manifestation; they were treated with streptomycin at the time of the second pleurisy.

It is of course unjustifiable statistically to compare 15 patients on the one hand with 85 patients on the other, but at least the morbidity trend is in keeping with Maclean's observations. Apart from statistical analysis, clinical observation of a patient with long-continued pyrexia indicates that there is a serious disease process at work. Such a patient is commonly laid very low by his illness, and, even if no overt tuberculosis develops, convalescence is protracted. It is possible that the pleurisy with effusion per se is not always the cause of the prolonged pyrexia; of the 15 patients observed, only 2 had a correspondingly prolonged effusion. One is tempted to postulate that the pyrexia may be due to the development, at sites other than the pleura, of tuberculous lesions which commonly, in the course of time, become clinically or radiologically evident.

4. Duration of Effusion.

Maclean (1948) believes that the prognosis worsens with increasing duration of the effusion. In the author's experience, it is often hard to decide when the effusion has absorbed; residual pleural thickening may simulate, both clinically and

radiologically a small effusion; short of further diagnostic thoracentesis, which is probably unjustifiable at that stage, it may be impossible to separate the two. Therapeutic aspiration of large quantities of fluid may influence the duration in some cases. A loculated collection of fluid, which often persists for a long time, is probably not comparable with non-loculated collections. On the whole, it seems undesirable to base prognosis on information which is subject to so many variables and which is therefore difficult to assess with accuracy.

5. Isolation of Tubercle Bacilli from the Fluid.

This factor must again vary according to the thoroughness with which efforts to isolate tubercle bacilli are made. Of the author's 100 cases, 40 were used in the bacteriological investigation described in Section III. Of the 40 fluids, 21 yielded a growth of tubercle bacilli on intensive Lowenstein-Jensen culture, while the remaining 19 yielded no growth. Of the 21 patients with positive fluid, 9 (42.9%) developed overt tuberculosis; of the 19 patients with negative fluid, 3 (15.8%) developed overt tuberculosis. The numbers are small and therefore the results are no more than suggestive. Further investigation, using a uniform and thorough technique on a large number of fluids, is indicated.

6. Miscellaneous.

Pinner and Moerke (1930) state that chemical,

cytological and serological data are not dependable prognostic criteria. Maclean (1948) states that a study of the family history in his cases gave no significant finding. In the author's series of cases, only 9 (9%) had radiological evidence of a primary tuberculous complex in the lung and/or hilar glands at the time of the effusion; in 1, the focus in the lung became progressive; in 1, fatal bronchogenic tuberculosis supervened; the remaining 7 patients pursued a clinical course in no way different from the average effusion patient without evidence of a primary complex, and have remained well on follow-up; nothing of prognostic significance can be deduced.

7. Influence of Adequate Convalescence.

This factor is mentioned last because, unlike the others, it cannot be evaluated at the time of the original illness. Trudeau (1939) treated 54 primary effusion patients in a sanatorium in the United States and claims that this strict regime lessened the tuberculous MORTALITY to a figure no higher than that of the ordinary population; examination of his figures, however, indicates that the tuberculous MORBIDITY was 11%, perhaps a disappointingly high figure in the circumstances. In Great Britain at the present time sanatorium accommodation is only rarely available for effusion patients, and even ordinary convalescent hospital accommodation is difficult to obtain in certain areas. In Edinburgh,

the position is particularly fortunate in that the Astley Ainslie Hospital has virtually unlimited accommodation for effusion patients. With the exception of the older age group patients, of whom a considerable number were discharged straight to their homes, a high proportion of the author's patients were given a period of from 3 to 6 months' convalescence at the Astley Ainslie Hospital under conditions closely approximating to those in a sanatorium. Even so, the tuberculous morbidity was high. It may therefore with justification be asked if the present system of convalescent care is good enough. Possibly it is not, but there is no means of knowing whether prolongation of convalescence to a year or more, even if it were possible, would make any difference to the ultimate prognosis. In the absence of such knowledge, it is probably not reasonable to insist on a period of longer than six months - assuming satisfactory progress in that time - with its detrimental effect on the patient's work, finances and morale, unless a study of other prognostic factors indicates the probability or possibility of subsequent relapse. It may be too that in the future the answer to the bad risk patient will lie more in specific anti-biotic and chemotherapy than in the somewhat doubtful measure of prolonged inactivity.

Prognosis in Relation to Life Insurance.

This is important from the point of view of the

patient and his relatives, although it does not of course concern the physician in his clinical care of the patient. Life Insurance companies vary in their attitude to the problem -

(a) Anderson (1928) believes that all recovered cases over 30 years of age who have regained their normal weight and in whom there is no family history of tuberculosis may be accepted at normal rates after five years have elapsed from the date of the original illness.

(b) Dublin and Marks (1932) - meeting of the Association of Life Insurance Medical Directors of America - state that at ages over 35 a few cases may be granted standard insurance after five years have elapsed.

(c) The principal medical officer of the Standard Life Assurance Company (1952) - personal communication - states

- i. No acceptance on any terms in first five years.
- ii. After five years accept at any age with loaded premium reducing to normal premium at the age of 45, provided that general health is good, family history is negative for tuberculosis and chest X-ray is negative.

It is probable that the bias in favour of older patients expressed in (a) and (b) is not justifiable in relation to present day information. The reducing, but not entirely absent, risk of relapse

after 5 years is clearly expressed in (c). Although Thompson (1946) - series of 190 cases - found that most patients who relapsed did so within 2 years and that no patient relapsed after 5 years, Frostad (1951) in a prolonged follow-up of a large series of 720 cases, found that 19% of relapses occurred after 5 years and that 16% of relapses with pulmonary, as opposed to non-pulmonary, tuberculosis occurred after 10 years.

Practical Applications.

1. Tuberculous morbidity and mortality following primary tuberculous pleural effusion are still distressingly high.
2. It is difficult to assess prognosis in the individual patient at the time of the original illness. There is, however, some evidence to show that the following factors worsen prognosis -
 - (a) Increasing age of patient.
 - (b) Presence of bilateral simultaneous or consecutive pleurisy with effusion.
 - (c) Prolongation of pyrexia beyond 4 weeks.
 - (d) Isolation of tubercle bacilli from the pleural fluid.
3. If any patient is to be selected for special care - e.g. prolonged sanatorium regime - or treatment - e.g. specific antibiotic and chemotherapy -, the presence of one or more of those factors should dictate his selection.

4. For follow-up and Life Insurance purposes, the risk of relapse is greatest in the first two years and is still considerable up to 5 years; after 5 years the risk is small but not entirely absent.

SECTION XIITREATMENT OF PRIMARY TUBERCULOUS PLEURAL EFFUSION

It is universally accepted that the broad principles of treatment should be those applicable to tuberculosis in general. The patient with pleural effusion, however, presents certain special problems not least of which is that the illness, although tuberculous in nature, must be managed throughout its course first in the ward of a general hospital and later at an ordinary convalescent hospital. With the existing shortage of sanatorium beds, this state of affairs is likely to continue for a long time to come. The following observations on treatment, based on the series of 100 consecutive cases already referred to in Section XI are therefore relevant to the problems encountered by the general physician, who must continue to act, *faute de mieux*, in place of the chest or tuberculosis physician.

1. Duration of Stay in General Medical Ward.

The shortage of beds is not confined to sanatoria, and it is therefore expedient that a patient with pleural effusion should not "block" a general medical bed for an undue length of time, especially when, as in Edinburgh, a suitable convalescent hospital exists. As a general rule, the patient is fit for transfer to the convalescent hospital when the axillary temperature has returned to normal.

TABLE 32100 Cases of Primary Tuberculous Pleural EffusionTime required for return of Axillary
Temperature to Normal

<u>Time in Days</u>	<u>No. of Cases</u>
0 - 7	38
8 - 14	23
15 - 21	13
22 - 28	11
29 - 56	9
56 +	6
	100

Table 32 indicates that in almost two-thirds of cases, transfer to the convalescent hospital can be arranged within 14 days. There is, however, a tendency among physicians to delay transfer for a period longer than that suggested, namely until pulse rate, E.S.R. and perhaps even the rectal temperature have also returned to normal. This delay is probably unnecessary, provided always that medical supervision will be available at the convalescent hospital. On average, when the axillary temperature has reverted to normal, the pulse rate is still 80-90 per minute and the E.S.R. around 30 mms. in the first hour. Although early transfer to the more suitable environment of the convalescent hospital is strongly advised, the patient with continuing axillary pyrexia is better retained since special management may be

required; an occasional patient whose axillary temperature has returned to normal must also be retained, usually on account of doubt regarding the diagnosis which may necessitate further hospital investigation; further, if while at the convalescent hospital, progress is unsatisfactory or untoward symptoms and signs arise, the patient should be readmitted to the general medical ward for reassessment.

2. Aspiration of Fluid.

Following admission to the general medical ward and the arranging of bed-rest, diet etc., the first problem in management of the patient usually concerns aspiration of the fluid. Although all physicians are agreed on the need for diagnostic thoracentesis, it is extraordinary how, despite accumulated experience over many decades in the treatment of this disease, controversy still exists about the desirability of, and indications for, subsequent aspiration. It is clearly impossible to lay down rules on the relatively small experience gained from 100 cases; it is proposed instead to set out the scheme, with observations thereon, adopted by the author and applied, as far as the physician-in-charge would permit, to every patient.

(a) Diagnostic Thoracentesis. This was done in all cases without delay to confirm the presence of fluid, to determine the nature of the fluid and to obtain a specimen for cytological, bacteriological and perhaps biochemical examination. Only a small quantity of fluid was removed.

(b) Relief of Dyspnoea. It is of interest that no patient on admission had dyspnoea severe enough to indicate therapeutic, as opposed to diagnostic, aspiration. Further, no patient had a subsequent increase in the quantity of fluid sufficient in degree to cause dyspnoea at rest. A few patients had moderate dyspnoea on admission, but this subsided rapidly with rest in bed and mild sedation. It is concluded that tuberculous effusion seldom requires immediate aspiration for mechanical reasons.

(c) Threat of tuberculous Empyema. In 2 cases, the finding in the fluid removed for diagnostic purposes of tubercle bacilli on DIRECT EXAMINATION of the stained smear indicated the presence of large numbers of bacilli and therefore the potential danger of tuberculous empyema. Repeated aspirations, removing increasing quantities of fluid, were considered justifiable. In one case, despite increasing turbidity of the initially clear fluid, pleural obliteration was successfully achieved. In the other case, also with initially clear fluid, a frank tuberculous empyema developed. It is suggested that the finding of tubercle bacilli on direct examination is an indication for repeated aspiration and, at the present time, intrapleural streptomycin.

(d) Further Diagnostic Aspiration. This was done in the following circumstances -

- i. Appearance of pleurisy with effusion on the contralateral side - 5 cases.
- ii. Recurrence of pleuritic pain with increasing

effusion on the same side - 4 cases. It was thought necessary to exclude developing tuberculous or secondary empyema.

iii. Pyrexia continuing for more than 3 weeks with persistence of fluid - 24 cases. Again it was thought necessary to exclude developing tuberculous or secondary empyema.

It is of interest that of the 28 cases re-aspirated because of ii and iii, no case had actually developed an empyema. It may be therefore that those indications are not strongly valid, but anxiety regarding them can be relieved only by further aspiration.

(e) Persistence of Effusion. It is stated in the standard Edinburgh text-book of medical treatment - Dunlop, Davidson and McNee (1949) - that "it is difficult to lay down hard-and-fast rules as to how long an effusion should be left before aspiration is undertaken, but if there are no signs of spontaneous reabsorption after 5 or 6 weeks, aspiration should be considered." It is commonly argued that if fluid is allowed to remain in the pleural cavity for more than 6 weeks, excessive deposition of fibrin on the pleural surfaces leads to gross fibrosis and a "captive lung".

In the author's series of cases, only 6 had an appreciable quantity of fluid left in the GENERAL pleural cavity after 6 weeks. As a trial, aspiration was not offered to those patients. In 5 of the

6, subsequent progress was entirely satisfactory with complete absorption of the fluid without clinical or radiological evidence of more than slight fibrosis. In the remaining patient, the fluid became loculated at the lateral chest wall (Fig. 90) and showed no signs of diminution after several months. Aspiration was now performed, but fluid was obtained with difficulty and marked fibrosis resulted. In a few cases, small quantities of fluid tended to persist in the interlobar fissures, but eventually absorbed satisfactorily.

Although significant fibrosis resulted from long persistence of fluid in only one case, it is unfortunately true that gross fibrosis occurred unexpectedly in four other cases. Each had an acute pleurisy with high temperature; fluid formed rapidly but did not persist unduly and there seemed no indication for more than diagnostic aspiration; in the course of time, however, flattening of the affected hemithorax became visible on clinical examination. In 1 case, in addition to fibrosis, calcification of the pleura occurred (Fig. 91). It is hard to explain the fibrosis in those cases. There was no evidence of pulmonary atelectasis. It may be that early and repeated aspiration would have prevented or minimised the fibrotic process; on the other hand, it is possible that the process was due not so much to the actual fluid as to unusually severe and diffuse pleural inflammation - and perhaps even

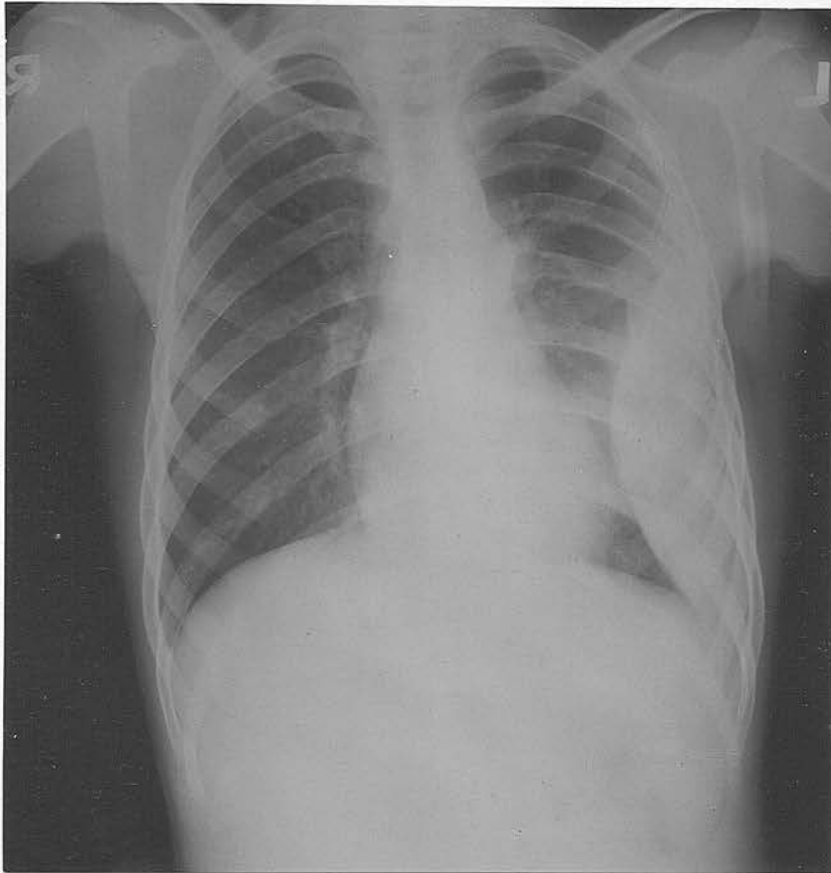


Fig. 90

Chest X-ray showing loculation of left pleural effusion at lateral chest wall. Marked fibrosis eventually occurred. It would seem advisable to aspirate such a loculus.

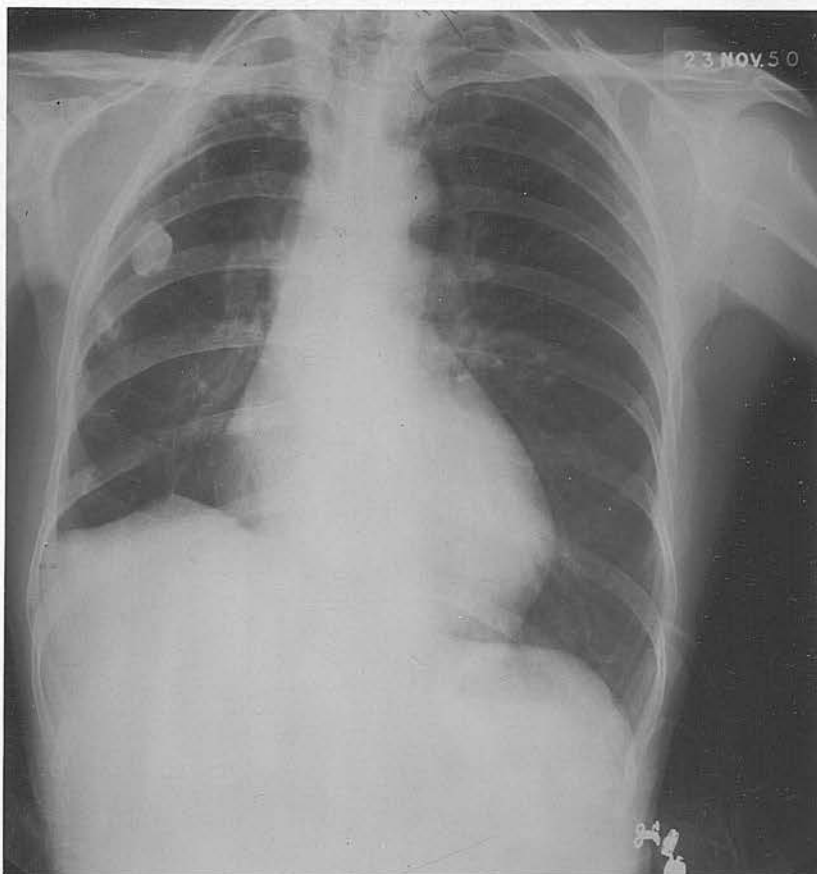


Fig. 91

Chest X-ray of a patient in whom marked pleural fibrosis occurred. In addition to the features of fibrosis, calcification of the pleura is seen.

caseation in view of the ultimate calcification observed in 1 case. 3 of the 4 patients regained considerable function of the affected hemithorax by means of intensive physiotherapy, but they remain candidates for "captive lung". The fourth patient escaped follow-up.

3. Air-Replacement of Fluid.

This procedure has rightly fallen into disrepute. It was originally introduced for two quite different purposes -

(a) To control a rapidly recurring effusion causing severe dyspnoea at rest.

(b) To treat, with the resultant pneumothorax, an underlying tuberculous lesion in the lung.

With regard to (a) it has been shown that primary tuberculous effusion seldom causes such mechanical embarrassment; if it should do so, repeated aspiration should be sufficient to control the situation.

With regard to (b) an increasing knowledge of the pathology of primary tuberculous effusion has shown that pneumothorax is fundamentally unsound in its treatment. The tuberculous lesion present is a primary complex with Ghon focus and glandular component. There is no pulmonary cavity which requires collapse therapy for its closure. Further, a pneumothorax normally obliterates itself in the presence of fluid. This is fortunate, since otherwise tuberculous empyema tends to occur. Tuberculous empyema supervened in the only case in the

author's series treated by air-replacement.

4. Treatment of Co-existing Primary Complex.

In 9 of the 100 cases, there was radiological evidence of a primary tuberculous complex at the time of the effusion; in 2 of the 9, both pulmonary and glandular components were visible; in 7, only the glandular component was visible.

As far as the pulmonary component of a primary complex is concerned, spontaneous healing with calcification nearly always occurs, and therefore no special treatment was adopted apart from more frequent serial X-rays to detect possible local progression. Progression occurred in 1 of the 2 cases, necessitating transfer to a sanatorium as a case of pulmonary tuberculosis.

As far as the glandular component is concerned, spontaneous healing is again the rule, although, in children, trouble may arise from bronchial compression and invasion causing pulmonary atelectasis - Roberts and Blair (1950); Jeune, Mounier-Kuhn, Béthenod and Potton (1951). In the author's cases, atelectasis was not encountered, probably because in adults both young and old, the bronchi are larger and more rigid and therefore not so easily obstructed. In the absence of atelectasis, no special treatment seemed indicated. It was noted that the enlarged hilar shadow required many months to regress, but this need not give rise to anxiety - Wallgren and Wegelius (1949).

In the unlikely event of the glandular component in the adult causing overt atelectasis in association with fluid, special treatment would seem to be indicated because of the risks of bronchiectasis and undue persistence of fluid in a pleural cavity with high negative pressure. The problem is what kind of treatment. Lorber (1950) and Jeune, Mounier-Kuhn, Béthenod and Potton (1951) have shown that streptomycin has no beneficial local effect on the glandular component of a primary complex. Bronchoscopy should probably be performed. If bronchial compression only is found, nothing can be done. If, in addition to compression, there is evidence of the gland having invaded the bronchus, obstructing secretions and granulation tissue can be removed - Jeune et al (1951) and streptomycin can be given to treat the tuberculous bronchitis - Young (1953).

5. The Place of Antibiotic and Chemotherapy.

It is felt that some comment must be made on this problem, although significant personal experience cannot be quoted because the series of cases was observed mainly prior to the introduction of streptomycin and P.A.S. (para-amino-salicylic acid).

The use of intra-pleural streptomycin in a series of 47 cases has been reported by Danopoulos and Mellissinos (1951). They recommend one or at most two injection of 2 Gms. of streptomycin in 20 mls. of sterile normal saline, and claim that in all but 4 of the cases rapid clearing of the effusion

occurred. Crofton (1952) - personal communication - and Young (1953) have also been impressed with the immediate results in small series of cases. While further work on this method of treatment is clearly indicated, it should be kept in mind that results are hard to assess since fluid may absorb rapidly without special treatment. If the fluid is found to contain numerous tubercle bacilli - see para. 2 (c) - intra-pleural streptomycin is certainly indicated. In the absence of numerous bacilli, it would at first sight seem unnecessary to inject streptomycin, but it may be that streptomycin is absorbed from the pleural cavity via the lymphatics and carried to sub-pleural, glandular and even bronchial foci of infection - Abello (1951) and Young (1953). Intra-pleural P.A.S. was employed by the author in 1 case, but a change from lymphocytic to polymorphous cytology suggested that undesirable pleural irritation had occurred.

Oral P.A.S. - 15 Gms. daily - was given as the sole therapeutic agent to 5 of the author's febrile patients. In 2, there was no response of pyrexia. In 3, pyrexia subsided rapidly, but there is no guarantee that this would not have happened spontaneously; even so, the 3 patients experienced a sudden increase in well-being and it was proposed at the time that oral P.A.S. might be used for febrile, toxic patients who were experiencing great discomfort from the mere presence of fever. Crofton (1952)

- personal communication - has found, however, that the giving of P.A.S. ALONE tends to encourage P.A.S. resistance of the tubercle bacillus which in turn appears to precipitate streptomycin resistance if and when it is necessary to employ the latter drug. This is a grave disadvantage of P.A.S. therapy, and it is therefore suggested that the drug should never be used as a sole therapeutic agent.

Parenteral streptomycin plus oral P.A.S. (S. + P.A.S.) is now firmly established as a satisfactory means of treating pulmonary and other forms of tuberculosis. With proper dosage schedules, the risk of streptomycin resistance developing is slight - Medical Research Council Investigation (1952).

With regard to primary tuberculous pleural effusion, the danger to the patient probably lies not so much in the effusion itself, but in foci of tuberculous infection in hilar glands, in the sub-pleural areas of the lung and perhaps in other organs of the body whence the bacilli have been carried by the blood stream. If the patient is fortunate, those foci heal; if not, overt tuberculosis develops in the lungs or elsewhere. It might well be argued, therefore, that S. + P.A.S. should be given, not to treat the effusion, but to attempt to eliminate those bacilli which are circulating in the blood stream and possibly establishing themselves, at the time of the effusion or later, at sites of future overt tuberculosis. On the other hand, it might with equal

justification be argued that S. + P.A.S. should be kept in reserve to treat overt tuberculosis if and when it appears. In the section on prognosis, it has been shown that certain features, viz. advancing years, long-continued pyrexia and the occurrence of bilateral pleurisy with effusion, tend to worsen the prognosis; in older patients particularly, there is suggestive evidence that haematogenous dissemination is not uncommon. It is therefore suggested that those features constitute indications for S. + P.A.S.; there is of course no proof that the therapy will be successful, but there is at least no valid reason for withholding it. One difficulty in the suggested scheme is that the younger patient with long-continued pyrexia cannot be treated until observation has shown that the pyrexia IS long-continued. This difficulty must exist, with the possible danger of delay, unless S. + P.A.S. is given to all cases irrespective of prognostic factors. The dosage schedule should be streptomycin 1 Gm. daily by intramuscular injection and P.A.S. 20 Gms. daily by mouth, for 3 months. Isoniazid has not been mentioned, because, at the time of writing, insufficient is known of its uses and dangers for it to be employed by a general physician.

6. Management at the Convalescent Hospital.

Little need be said about this. The regime should approach as closely as possible to that of the sanatorium, with good food, fresh air and graduated

exercise. One point requires special mention: the X-ray equipment of a convalescent hospital is frequently archaic and therefore unsuitable for the detection of early pulmonary lesions; if necessary, the patient should return to the general hospital once a month for a good quality X-ray of chest.

7. The Follow-up Period.

As indicated in Section XI, this should extend for at least five years, special care being required for the first two years. At each visit, the main essential is again a good quality X-ray of chest, although untoward symptoms and signs may require appropriate investigation for tuberculosis of organs other than the lungs. Further discussion is not required, except on one point, namely the responsibility for follow-up.

The simplest method is to notify each patient as a case of tuberculosis, thus transferring responsibility to the organisation of the local chest physician - formerly tuberculosis officer. Indeed, when the tubercle bacillus has been isolated from the pleural fluid or from the sputum (gastric juice), notification becomes a statutory duty, although in only a minority of patients does this condition apply. Apart from follow-up, an advantage in notification is the machinery for examination of the patient's "contacts". When the tubercle bacillus has not been isolated, there is a natural reluctance on the part of the physician to "brand" the patient as tuberculous, and, for this reason alone, notification is

not always practised in the Royal Infirmary of Edinburgh. From the point of view of the patient, notification is naturally regarded with disfavour since it means attending at a chest clinic - formerly tuberculosis dispensary - along with established cases of tuberculosis; indeed this is the great disadvantage of notification, because in time, the disgruntled patient, wishing to remove himself from any association with tuberculosis, may cease to attend.

It is difficult to reconcile the advantages and disadvantages of notification. It may be that there is room for a modified scheme whereby the chest clinic is responsible for examination of contacts while the general hospital unit is responsible for follow-up of the patient. On the other hand, it may be that the objections to notification are imaginary and out-of-date in relation to the modern function of a chest clinic which no longer deals entirely with broken-down chronic cases of tuberculosis. The fact remains that some effusion patients at the present time fall between two stools and thus receive no follow-up care. This should not be allowed to happen. If the physician does not care to notify the patient, which is undoubtedly the easiest and safest course, he must assume the responsibility for adequate follow-up of the patient and examination of contacts.

THE PLEURAL EFFUSION UNIT

Primary tuberculous pleural effusion is still a common disease, and it is obvious that a hospital or unit set aside solely for such patients would have no difficulty in filling its beds. The first unit in Great Britain of this type was opened at the Queen Mary Hospital, Sidcup, Kent in 1947. Through the kindness of Dr. Harley Williams of the National Association for the Prevention of Tuberculosis, the author was permitted to visit this unit for a few days in April, 1951, when the following observations were made.

The Queen Mary Hospital is a general hospital situated in a semi-rural area in South London. It was formerly an E.M.S. hospital and the buildings are therefore of a semi-permanent character, but well-equipped. The effusion unit has 120 beds contained in four wards, two male and two female. Each ward has a separate nursing staff, and it is interesting to note that the male wards are run entirely by male nurses, including the ward "Sister". This arrangement has been found most satisfactory, especially during the shortage of nurses and from the point of view of discipline in long term cases.

The medical staff is under the control of the medical superintendent and consists of:-

1. A visiting consultant in diseases of the chest, who visits once a week.
2. A registrar who is responsible for the day-to-day

running of the unit and for case writing. The duties of the registrar are very heavy. He is full-time on the unit, but is required to do all the work which would normally, in a general hospital ward, be done by the house officer. Because of this and the limitation in variety of work, it is often difficult to obtain a suitable candidate for the registrar post.

Ancillary services are readily available in the hospital, including fluoroscopy, radiology, tomography, bacteriology, biochemistry and the E.N.T. Department, where bronchoscopy can be performed.

Patients are admitted from all over England, most coming from the London area. Only patients with effusions thought to be due to primary tuberculous infection are admitted, but sometimes the effusion proves to have a different aetiology and hence all are carefully investigated on admission. There is a proviso that no case with tubercle bacilli in the sputum is admitted, thus avoiding conversion of the unit to something like a sanatorium. If bacilli subsequently appear in the sputum, the patient is immediately transferred to a sanatorium.

The management and treatment of the patient are along conventional lines. Rest in bed is enforced until the general condition is satisfactory, and temperature, pulse and E.S.R. are normal. Thereafter, progress is graded in units of hours out of bed - from one hour to eight hours. After the five hour stage, week-end leaves at home are granted and the patient attends daily at the occupational therapy

unit. There is no doubt that the occupational therapy unit and the week-end leave system do much to alleviate boredom and discontent after the patient has become fit. When the patient is up eight hours per day, he is sent to the Convalescent Home attached to the Hospital for a period of two to three months. This Home corresponds roughly to the Astley Ainslie Hospital in Edinburgh, except that patients are much more advanced in convalescence when they are transferred than is the case in Edinburgh. Thereafter the patient is sent home.

It seemed to the author that the unit, although setting a high standard in the treatment of effusion patients, failed to utilise fully the opportunities for research available from the large number of admissions. The registrar pointed out that research is hampered by two circumstances -

1. Patients are admitted at a varying and often prolonged time after the onset of illness; this causes difficulty in standardising and comparing different methods of investigation and treatment.
2. Absence of follow-up; no patient is seen again after discharge and no effort is made to obtain follow-up information by other means.

In Sections XI and XII, it has been pointed out that many problems regarding the prognosis and treatment of effusion patients require elucidation. The organisation at Sidcup, with modifications to ensure early admission of patients and adequate follow-up

information, would provide the ideal means for planned and controlled research into those problems.

Apart from research, it may be asked if effusion units are essential or even desirable as part of the Hospital Service in Great Britain at the present time. It is probable that in most areas they are not essential, since the average effusion patient is seldom denied a minimum of care and attention, first in a general medical ward and later at a convalescent hospital. It is therefore unlikely that Regional Hospital Boards, in face of present financial difficulties, would receive enthusiastically suggestions for further strain on their resources. Indeed, in the past year, the only effusion unit to exist in Scotland - at Bridge of Earn - has been closed down by the Eastern Regional Hospital Board. The problem must also be regarded in the light of the wider problem of tuberculosis in general, including the prevention of tuberculosis. Perhaps in years to come the increasing use of mass radiography, B.C.G. vaccination and other measures will to a large extent eliminate dangerous primary infections and their consequences, including primary pleural effusion.

SECTION XIIISummary and Conclusions

1. By means of Leishman stained films, a study was made of the distribution of lymphocytes, polymorphs and serosal cells in 146 serous pleural fluids of varied aetiology. From the practical diagnostic point of view in the individual case, it is shown that the only reliable finding is a high percentage of serosal cells which indicates either neoplasm or transudate. A high percentage of lymphocytes is of little diagnostic value. A high percentage of polymorphs favours simple inflammation or tuberculosis to the exclusion of neoplasm and transudate.

2. As a corollary to the Leishman film study, reference is made to the phenomenon of pleural eosinophilia. Pleural eosinophilia, while occurring in a variety of other conditions, is uncommon in tuberculosis and excessively rare in neoplasm, thus being of some diagnostic value.

3. A study was made of 111 pleural fluids - from 90 patients - sent to a Pathology Department for opinion regarding the presence of malignant cells. It was found that numerous "false positives" occurred in the routine reports by the pathologist. Using paraffin sections stained with haematoxylin and eosin, the causes for error were investigated and criteria for the cytological diagnosis of malignancy were

established. This study is presented with illustrative photomicrographs. Provided that the pathologist is conservative and strict in his criteria, the cytological diagnosis of malignancy is of definite, although limited, value to the clinician.

4. A routine technique for the isolation of tubercle bacilli from patients with primary tuberculous pleural effusion was found to be unsatisfactory. A more thorough technique, employing relatively large numbers of Lowenstein-Jensen cultures, was investigated in a series of 40 patients. It is concluded that, if search for tubercle bacilli is to be made at all, it should be made with a thorough technique giving a reasonable number of "positives". While it would obviously be desirable to use the thorough technique in all suspected tuberculous patients, lack of laboratory space and financial stringency may justify its limitation to the investigation of patients in whom special difficulty in diagnosis exists.

5. A study was made of 73 patients over 40 years of age presenting with serous pleural effusion of initially uncertain aetiology. It was established that primary tuberculous pleural effusion is not uncommon in those older patients, in whom there is perhaps too great a tendency to diagnose malignant disease.

6. Cardiac pleural transudate (hydrothorax) may present considerable difficulty in diagnosis. Five cases, including one of interlobar hydrothorax, are discussed with special reference to features of diagnostic importance.

7. Pleural effusion is discussed in relation to the collagen diseases. Acute disseminated lupus erythematosus may begin with an episode of pleurisy with effusion. In rheumatoid arthritis, pleural effusion MAY be part of the rheumatoid process, but other possibilities must be considered before this conclusion is reached. If acute rheumatic pleurisy exists, it is exceedingly rare; evidence is presented to illustrate the dangers of diagnosing rheumatic pleurisy. In scleroderma, a specific pleural lesion may occur with resultant "oedema" of the pleural cavity. In periarteritis nodosa, pleurisy and pleural effusion are rare and probably always due to pulmonary infarction. In general, when pleurisy is associated with joint symptoms and/or signs, the syndrome of tuberculous rheumatism should be kept in mind.

8. Observations are presented on pleural effusion in reticulosis. The type of reticulosis most commonly associated with pleural effusion is Brill-Symmer's Disease (lymphoid follicular reticulosis).

9. Post-pneumonic sterile serous effusion is a relatively new condition causing considerable difficulty

in diagnosis in hospital practice when the patient has not been observed from the beginning of his illness. Helpful clinical and radiological features are evaluated. On occasions, it is necessary, in the interests of the patient, to regard such an effusion as tuberculous in origin.

10. Pleural effusion due to pulmonary infarction resembles in many respects that due to malignant disease, especially bronchial carcinoma. It may not be possible immediately to differentiate the two; in this event, if reasonable suspicion of pulmonary infarction exists - i.e. if a source for an embolus can be found - treatment with anti-coagulants should be instituted in the hope that the suspicion is correct.

11. While in the investigation of the older age group patient presenting with serous pleural effusion due regard must be given to other conditions discussed above, the main problem concerns the differentiation of tuberculosis and neoplasm. Emphasis is placed on the clinical, cytological and, to a lesser extent, the bacteriological approach to this problem. It is shown that tuberculosis, which requires immediate treatment, is in the background as frequently as neoplasm. For this reason, recourse to thoracic surgical investigation is indicated only when a strong suspicion of neoplasm exists.

12. In the corresponding younger age group patient, tuberculosis is the cause in 90% of cases. Unless, therefore, there are unusual features causing suspicion of an aetiology other than tuberculosis, extensive investigation is unnecessary. In this connection, APPARENTLY incompatible features leading the diagnosis away from tuberculosis are reviewed and fallacies are discussed.

13. Approximately 30% of patients with primary tuberculous pleural effusion subsequently develop overt tuberculosis in the lungs or elsewhere. An attempt is made to analyse factors which influence prognosis and which may be assessed at the time of the original illness. Increasing age, prolonged pyrexia and the occurrence of bilateral pleurisy with effusion are unfavourable factors.

14. Observations are made on the treatment of primary tuberculous pleural effusion.

(a) The introduction of antibiotic and chemotherapeutic agents may mean that treatment in the future will be more effective than it has been in the past. Suggestions are made regarding the selection of patients for treatment with those agents.

(b) Indications for the aspiration of fluid are discussed. Although certain definite points emerge, the prevention of residual fibrosis remains a problem. There is a suggestion that long persistence of

the effusion may not be the only important factor in the production of fibrosis; fibrosis may occur in effusions of short duration, the cause being obscure. It may be that a trial of early and repeated aspiration in all cases is justified.

(c) A certain number of patients escape follow-up because of uncertainty regarding the responsibility for this. Each physician must decide whether the responsibility is his or that of the local chest physician.

15. The institution of special pleural effusion units with their opportunities for controlled research would solve many problems at present outstanding in the treatment of primary tuberculous effusion. The organisation of the unit at Sidcup, Kent is described, along with suggested improvements.

SECTION XIV

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